Queensland University of Technology

Impact of Socio-Ecological Variability on the Transmission of Malaria in Yunnan Province, China

By

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Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

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To my husband, Guojun

our son, Jiayi

and my family members

Abstract

Malaria is one of the most serious and widespread mosquito-borne diseases (MBDs) globally. China has successfully controlled malaria transmission with a sharp decrease of malaria incidence in the past decades. However, malaria transmission is still severe in some remote and poor endemic regions such as Yunnan Province in south China. This research aims to explore the spatio-temporal patterns of malaria in Yunnan Province, identify the high risk areas of the disease, and assess the relationship between socio-ecological factors and malaria in these high risk areas.

Visualisation of malaria incidence and mortality using GIS mapping techniques reveals the spatio-temporal variation of malaria at a county level over time. The results show that the incidence and mortality of malaria have decreased gradually and varied with space and time. The results also show the majority of malaria cases and deaths concentrated in western Yunnan. Spatial cluster analyses were performed to identify high risk areas along the China-Myanmar border in western Yunnan over four periods (1991–1995, 1996–2000, 2001–2005, 2006–2010) (relative risks (RRs) = 23.03–32.06, $p < 0.001$) and along the China-Laos/China-Vietnam borders in southern Yunnan (RR = 2.33, $p < 0.01$) which was only observed in the first period (1991–1995). The findings imply that malaria remains a serious health threat in these "hotspot" regions. High risk periods of malaria transmission occurred in autumn (RR = 58.91, $p < 0.001$) and summer (RR = 31.91, $p < 0.001$).

Distributed lag non-linear model (DLNM) with Poisson link was used to estimate the effects of climate variability, on weekly malaria cases, in the identified high risk

areas along the China-Myanmar border. The results show that temperature and rainfall were statistically significantly associated with *Plasmodium vivax* (*P.v*) and *Plasmodium falciprum* (*P.f*) while there was no apparent association between relative humidity (RH) and *P.f.* A 1 °C increase in minimum temperature was associated with the highest effect at lag 7 weeks for *P.v* (RR = 1.03 (95% CI, 1.01, 1.05)) and 6 weeks for *P.f* (RR =1.07 (95% CI, 1.04, 1.11)). A 10-mm increment in rainfall was associated with the highest effect at lag 3 weeks for both *P.v* (RR = 1.03 (95% CI, 1.01, 1.04)) and *P.f* (RR = 1.04 (95% CI, 1.01, 1.06)); and a 10% rise in RH with the highest RR of 1.24 (95% CI: 1.10, 1.41) at lag 5 weeks for *P.v*.

In this study, multi-variable regression models were used to integrate datasets on climatic, socio-economic, ecological factors and malaria incidence and to assess if the surveillance indicator, slide positivity rate (SPR), can be used to estimate malaria incidence in Mengla County along the China-Laos/China-Myanmar borders. The results show that, without SPR, the model could explain only 54% variation of the malaria incidence using 3 other independent predictors (i.e. Tmax, income and humidity), whereas 95% variation of the malaria incidence was explained after SPR was added to the model. These findings indicate that malaria transmission is driven by a range of socio-ecological factors. SPR is a useful indicator to estimate the malaria incidence in this region and can be used to validate malaria surveillance systems in China.

Little research has been done on the association between socio-ecological variability/changes and malaria transmission in Yunnan. This research examined spatio-temporal patterns of malaria transmission, identified high risk areas and periods of the disease, and evaluated the relationship between socio-ecological factors and malaria transmission. The findings may provide important information for further investigation of risk factors of malaria transmission in this region and for public health planning, decision making and formulating surveillance-response strategies to control and prevent this disease not only in China, but also in other countries facing a similar situation of endemic malaria. In addition, the methods developed through this research may have wide implications for other mosquito-borne diseases.

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Abbreviations

Abbreviation	Description
AIC	Akaike’s Information Criterion
China CDC	China Center for Disease Control and Prevention
CI	Confidence Interval
DALY	Disability-adjusted Life Years
DW	Durbin-Watson
DLNM	Distributed lag nonlinear model
GIS	Geographical Information System
GPS	Global Position System
ICD	International Classification of Diseases
IPCC	Intergovernmental Panel on Climate Change
MEWS	Malaria Early Warning Systems
MBD	Mosquito-Borne Disease
NDVI	Normalized Differenced Vegetation Index
NMEP	National Malaria Elimination Programme
NNDSS	National Notifiable Diseases Surveillance System
RR	Relative Risk
RS	Remote Sensing
SDSS	Spatial Decision Support System
SARIMA	Seasonal Auto Regression Integrated Moving Average
SATSCAN	Spatial, Temporal or Space-Time Scan statistics
SCF	Seasonal Climate Forecasts
YLD	Year Lived with Disability

Publications by the candidate

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1. **Bi Y.,** Hu W., Liu H., Xiao Y., Guo Y., Chen S., Zhao L., Tong S. Can slide positivity rates predict malaria transmission? Malaria Journal, 2012, 11:117
2. **Bi Y.,** Hu W., Yang H., Zhou XN, Yu W., Guo Y., Tong S. Spatial Patterns of Malaria Reported Deaths in Yunnan Province, China. American Journal of Tropical Medicine and Hygiene, 2013, 88(3):526-535
3. **Bi Y.,** Yu W., Hu W., Lin H., Zhou, XN, Guo Y., Tong S. The effects of climate variability on malaria transmission in Yunnan Province, China. Invited to revise by *Parasite & Vecotors*

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4. Lin, H., Lu, L., Tian, L., Zhou, S., Wu, H., **Bi, Y.,** et al. Spatial and temporal distribution of *falciparum malaria* in China. Malaria Journal, 2009, 8:130
5. Yu, W., Mengersen K., Dale, P., Ye, X., Guo, Y., Turner, L., Wang, X., **Bi, Y.**, Mcbride, J., Machenzie, J. and Tong, S. Projecting future transmission of malaria under climate change scenarios: Challenges and research needs. Under review
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7. Xu, Z., Sheffield, P., Su, H., Wang, X., **Bi, Y.,** Tong, S. The impact of heat waves on children's health: A systematic review. *The International Journal of Biometeorology*, March 2013

Conference presentations

8. **Yan Bi**, Wenbiao Hu**,** Huaxin Liu, Yujiang Xiao, Yuming Guo and Shilu Tong. Towards malaria risk prediction using socio-ecological data and slide positivity rate.

   Poster presentation.

   2010 Institute of Health and Biomedical Innovation (IHBI) conference, Queensland University of Technology. Gold Coast, Australia, 25-26th November, 2010.

9. **Yan Bi**, Wenbiao Hu**,** XiaoNong Zhou and Shilu Tong. Assessing high risk clusters of malaria mortality along border areas in south China.

   Poster presentation.

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10. **Yan Bi**, Weiwei Yu, Wenbiao Hu, Hualiang Lin, Xiao-Nong Zhou, Yuming Guo and Shilu Tong. The lagged effects of temperature on malaria in the high risk area of Yunnan, China.

    Oral presentation.

    Mosquito Control Association of Australia Symposium (MCAA) 2012 conference, Queensland Institute of Medical Research (QIMR). Gold Coast, Australia, 10-12th September, 2012.

Chapter 1: **Introduction**

1.1 Introduction

1.1.1 The burden of malaria in the world

Malaria is one of the most serious vector-borne diseases (VBDs) and remains a leading cause of morbidity and mortality and a major health burden in many developing countries (Sachs *et al.* 2002; Guinovart *et al.* 2006; Alonso *et al.* 2013). Despite more than 100 years of control efforts (Guinovart *et al*. 2006), epidemics of malaria still occurred in 104 countries in 2012 (World malaria report 2012). A global distribution of malaria (Figure 1.1) shows that many countries in Africa, South America, Eastern Mediterranea, South-Eastern Asia and Western-Pacific are still in malaria endemic regions. In 2011, there was an estimation of about 216 million malaria cases and approximately 665,000 deaths. International funding for malaria control increased sharply from less than US$ 100 million in 2000 to US$ 1.84 billion in 2012 (WHO 2012). Hay et al. (2004) estimated that although the number of regions where malaria transmission occurs has reduced from 1900 to 2010, with land area ranged from 77 to 39 million km^2 and the population exposing at risk has grown from 890 million to 3,410 million worldwide. The largest populations at risk of malaria have been found in the South-East Asia and Western Pacific regions (Snow *et al.* 2005). Malaria usually occurs in countries and areas located in tropical and subtropical zones. Malaria is one of the most important causes of year lived with disability (YLDs), with 433 and 498 per thousand of YLDs at all ages in 1990 and 2010, respectively (Vos *et al.* 2012). The cost of malaria intervention was estimated using disability-adjusted life years (DALYs) to be USD $2-24 per DALY on average, and the burden of malaria was 35 million DALYs (Laxminarayan *et al.*

2008). Malaria becomes a heavy burden of disease and a threat to global prosperity, economic growth and development (Sachs *et al*. 2002). In some countries with a heavy malaria burden, the disease may account for as much as 40% of public health expenditure, 30 to 50% of inpatient admissions, and up to 50% of outpatient visits (WHO 2002).

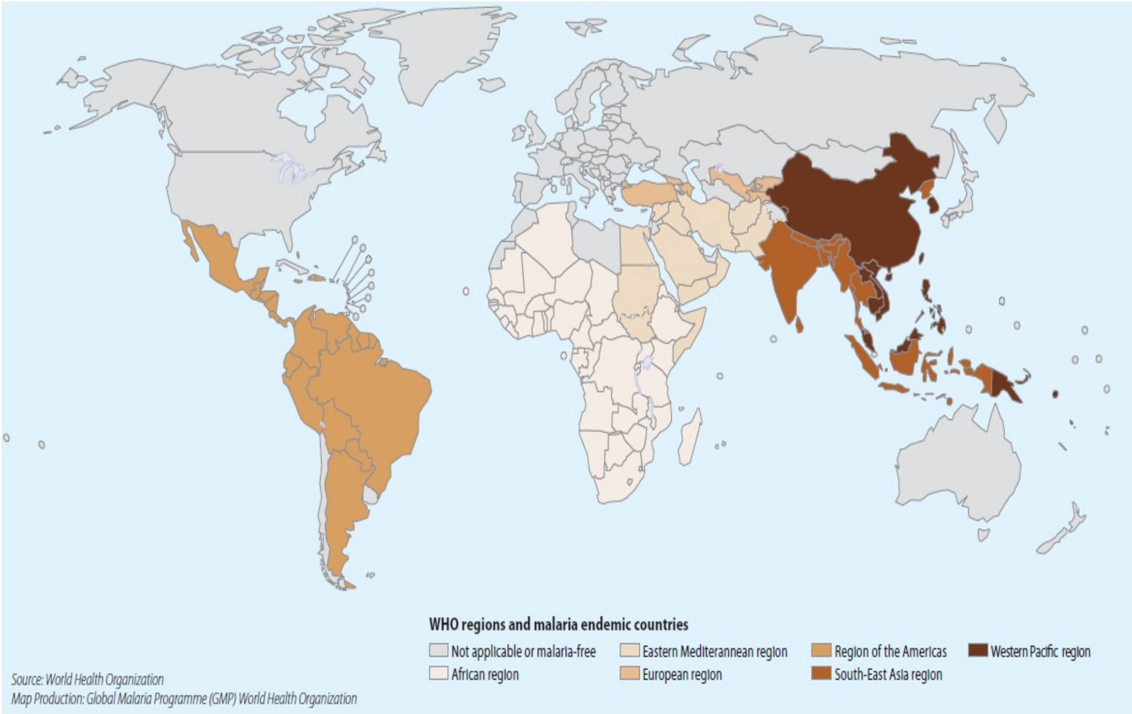


Figure 1.1 Distribtuion of world malaria
(World Health Organization 2012)

1.1.2 Malaria situation in China

Over past decades, the number of malaria cases in China has declined from 30 million in 1949 to 4,479 in 2011. The annual malaria incidence steeply decreased from 600/10,000 in 1949 to 0.03/10,000 in 2011 (Zhou *et al.* 2010; Xia *et al.* 2012). However, malaria transmission is still severe in some remote and poor endemic regions, such as, the Yunnan border areas in southern China and the central part of China, for instance, Anhui and Henan Provinces. Malaria outbreaks happen each year. For example, in 2006, malaria outbreaks resulted in 55,609 cases in four provinces, namely Anhui (34,984 cases), Yunnan (15,532 cases), Henan (5,093 cases) and Guizhou (515 cases) (Zhou *et al.* 2007).

Two types of malaria parasites, *Plasmodium vivax* (*P.vivax*) and *Plasmodium falciparum* (*P. falciparum*), are prevalent in China (Figure 1.2). The other two plasmodium species of *P. malariae* and *P. ovale* were sporadically reported with 71 cases in 2011, in which one case was local infection and 70 cases were overseas (62) and interstate (8) imported infections. In 2011, 40 cases of mixed infection of *P.vivax and P. falciparum* were reported. *P.vivax* is the dominant species and exists in 27 out of 31 provinces in China. Overseas-imported cases (>65%) have recently become a major source of malaria infections and have been widely distributed in China. For example, in 2011, overseas-imported *P.vivax* and *P. falciparum* cases accounted for 57% (1,183/2,075) and 96% (1,414/1,472) of all *P.vivax* and *P. falciparum* cases, respectively, which impacted more than 21 provinces across China. More than 80% of all malaria cases were laboratory confirmed in China. China is facing an increasing risk of imported malaria infections, particularly in its border areas and the regions having labor force output to the high malaria-endemic countries (Zhou *et al.* 2011; Xia *et al.* 2012).

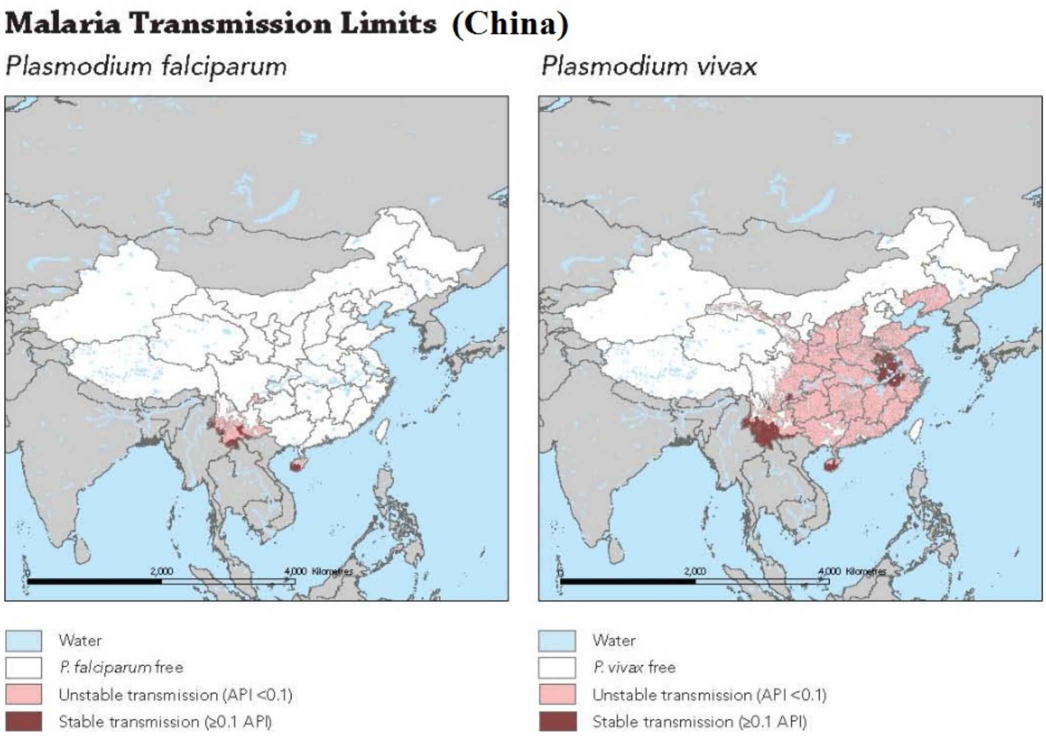
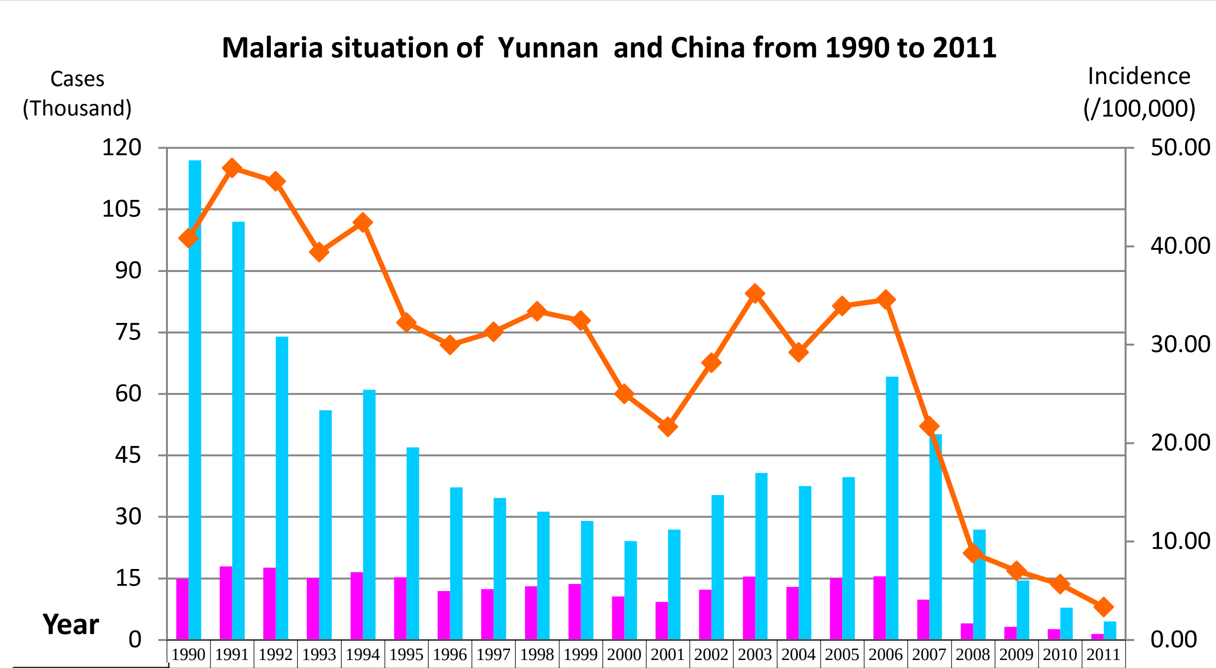


Figure 1.2 Malaria distribution of *Plasmodium falciparum* and *Plasmodium vivax* in China

(Atlas of the Asia Pacific Malaria Elimination Network, 2011)

1.1.3 Malaria situation in Yunnan Province

Yunnan Province is located in southern China bordering Myanmar in the west and Laos and Vietnam in the south. Historically, Yunnan was a malaria hyper-endemic area and suffered enormously from the threat of malaria with an annual number of cases between 140,000 and 420,000; incidences between 82.78/10,000 and 244.12/10,000 from 1952 to 1956 (Committee of Malaria Control and Prevention of China 1991). Even though malaria transmission in China has been greatly reduced since the 1990s, Yunnan remains to be an endemic region (Figure 1.3). The number of malaria cases in Yunnan was the highest in China and accounted for 34% of the total cases in the country in 2011 (Xia *et al.* 2012). In 2007, Yunnan had the highest number of malaria deaths in China (Zhou *et al.* 2008). In 2005 and 2006, the number of malaria deaths in Yunnan accounted for more than 80% of the total deaths in China (Zhou *et al.* 2006; Zhou *et al.* 2007). Among the 1,191 counties having malaria cases, three counties had an incidence of more than 10/10,000, two of them (i.e., Ruili (28/10,000) and Yingjiang (14/10,000)) from Yunnan Province (Zhou *et al.* 2011). In 2011, overseas-imported malaria infections accounted for more than 70% (1,084/1,522) of all malaria cases in this province. The major reasons may include the population movement between provinces and across international borders, which has greatly increased through roads, water, air, family reunions during the holidays, tourism and border trade. Yunnan suffers from a heavy burden of malaria transmission in China with rising mobile population along the border areas. Yunnan also faces an increasing risk of imported malaria infections from neighbouring countries.



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Cases(Yunnan)	14.9	17.9	17.6	15.1	16.5	15.3	11.9	12.4	13.1	13.6	10.6	9.28	12.2	15.4	12.9	15.1	15.5	9.8	4.0	3.2	2.6	1.5
Cases(China)	117	102	74	56	61	47	37.2	34.6	31.3	29	24.1	26.9	35.3	40.7	37.5	39.7	64.2	50.2	26.9	14.5	7.9	4.5
Incidence(Yunnan)	40.82	47.95	46.60	39.41	42.42	32.24	29.97	31.30	33.38	32.44	25.00	21.64	28.16	35.20	29.22	33.93	34.58	21.71	8.80	7.01	5.66	3.33

Figure 1.3 Time series distribution of malaria in Yunnan and China, 1990−2011

1.1.4 Transmission of malaria

Malaria is a life-threatening parasitic disease transmitted by infected *Anopheles* mosquito. Parasites from the *Plasmodium* genus enter the human body when an infected mosquito takes a blood meal. Parasites multiply in the human liver and bloodstream. After a period of about 7 to 14 days, the patient can have typical malaria symptoms like fever, headache, sweats, chills and vomiting (Bureau of Endemic Diseases Control of People's Republic of China 1998). Malaria can be prevented and cured. There are five *plasmodium* species which infect humans: *P. falciparum (P.f)*, *P. vivax (P.v)*, *P. malariae*, *P. ovale* and *P. knowlesi*. Among them, *P. f* and *P.v* are the most common and *P. f* is the most deadly. *P.v* is less dangerous although more widespread. The other species are found much less frequently. A new species, *P. knowlesi,* is reported and prevalent in southeast Asia which can cause severe infections in humans. For both *P. vivax* and *P. ovale*, clinical relapses may occur after the first infection. The reason could be that these new episodes arise from dormant parasites in the liver known as hypnozoites, which are absent in *P. falciparum* and *P. malariae.* Special treatment targeting at these liver stages is required for a complete cure (WHO 2012; WHO 2013). The intensity of transmission depends on factors related to the parasite, the vector, the human host, and the environment that are involved in the transmission cycles of malaria and making its ecology complex. A variety of factors are recognized to influence the transmission of malaria. For example climatic variables (e.g. temperature and rainfall) restrict the distribution and transmission of malaria both spatially and temporally (Craig *et al.* 1999; Beck *et al.* 2002; Lindsay *et al.* 1998; Tanser *et al.* 2003). Also, other factors such as human activities, socioeconomic status, vector control programs and environmental changes may also affect the spread of this disease (Hay *et al.* 2002; Small *et al.* 2003).

1.1.5 Spatio-temporal modelling

In epidemiology, the transmission of disease can be investigated through the distributions of person, place and time. Any disease can be described with these three parameters. Health professionals often need to understand disease trends, identify causes and make decisions efficiently according to the disease distributions of time, location and population (Jiang *et al.* 2003). It is fundamentally important for epidemiologic researchers to analyse spatial relationships of disease transmission (Hightower *et al.* 1998). Geographic Information System (GIS) and spatio-temporal modelling potentially have great implications in characterising malaria transmission, and have been used as important tools for better understanding the spatial variation of malaria and its relationship to socio-ecological factors and malaria surveillance (Booman *et al.* 2000; Clarke *et al.* 1996; Kitrol *et al.* 1994; Martin *et al.* 2002; Tanser *et al.* 2002).

GIS is particularly well suitable for providing visual, spatial-temporal maps for disease patterns, assisting to identify high risk locations and periods of disease. The most important and powerful function of GIS is the spatial analysis, which includes visualisation, exploration and modelling. Visualisation is able to show maps describing the dynamic change of disease patterns over space and time, and also display the results of traditional statistical analysis to assist further epidemiologic research. Exploratory data analysis can provide statistical methods for epidemiology and public health to identify space-time clusters or "hot spots" of disease. Modelling tests hypotheses about disease causation, the nature and processes of disease transmission. Model building includes the integration of GIS with standard statistical and epidemiologic methods. These procedures can be assisted with the use of GIS (Clark *et al.* 1996; Pfeiffer *et al.* 2008).

The transmission patterns of malaria are sensitive to socio-ecological conditions. For example, malaria has strong spatial and temporal patterns, because mosquito vector(s) transmit *plasmodium* parasites and the density and longevity of the mosquitoes depend on a range of environmental and ecological factors, e.g. temperature, rainfall, mosquito larval habitats. GIS and spatial-temporal modelling methods can be used to display and demonstrate causal relationships of disease (Clarke *et al.* 1996; Pfeiffer *et al.* 2008). The application of these approaches is increasingly used in malaria surveillance and risk management (Kitrol *et al.* 1994; Hightower *et al.* 1998). It is anticipated that the analyses of spatio-temporal relationships between risk factors and disease will improve our understanding of biological/ecological mechanisms of malaria outbreaks and transmission, and will assist public health authorities to develop a scientifically sound surveillance system for this disease.

1.2 Research aims and objectives

1.2.1 Aims

This research aims to explore the patterns of malaria, identify the high risk areas of the disease, and assess the relationship between malaria and potential socio-ecological risk factors, e.g. climatic variables, microscopy indicator, income and human population.

1.2.2 Objectives

The specific objectives of this research are to:

1. Visualise the spatial and temporal patterns of malaria in Yunnan Province, China.

2. Identify high risk locations and periods of malaria in Yunnan Province, China.

3. Develop spatio-temporal models to assess the effects of risk factors on malaria transmission.

1.3 Significance of research

This study is important because malaria continues to be a serious problem. For example, this completely preventable and treatable disease caused an estimated 655,000 deaths worldwide in 2010 (WHO 2010). About 560,000 of the victims were children under five years of age, which means that malaria killed one child every minute (WHO 2012). In China, the risk of malaria transmission remains in Yunnan Province, particularly along the border area. The overseas-imported malaria cases are also increasing in this region.

This research aims to identify spatio-temporal clusters of malaria and quantify the relationships between socio-ecological factors (e.g. climatic variables, microscopy indicator, income and human population) and malaria. The identification of high risk locations and periods of malaria incidence/mortality in the border area in Yunnan Province, southern China, will provide important information for further investigation of risk factors of malaria transmission in this region. Increased understanding of the association of socio-ecological variables with the transmission cycle of malaria in high risk areas, will help public health planning, decision making and formulating surveillance-response strategies to control and prevent the wide spread of this disease. This is also the first attempt to integrate socio-ecological factors and surveillance data to estimate the effects on these factors on malaria incidence in high risk areas in Yunnan. It may contribute to the growing literature on the assessment of hot spots and potential impacts of socio-ecological changes on the transmission of malaria. In addition, the methods developed through this research may have wide implications for other mosquito-borne diseases, and the findings of this research may also be applicable to countries with a similar problem of malaria transmission.

1.4 Structure of the thesis

This thesis includes seven chapters, which are structured as follows:

Chapter 1 introduces the background, aims, specific objectives and hypotheses of this research.

Chapter 2 reviews the literature on application of GIS and spatial-temporal approaches used in malaria research, and reviews previous research findings on the risk factors for malaria transmission.

Chapter 3 describes the research design and methods including choosing of the study area, data collection and management, and data analysis protocols.

Chapters 4-6 include three manuscripts. Two of them have been published in peer-reviewed journals and the third manuscript is under submission. They are presented in the publication style. In these chapters, I intend to address the hypotheses and achieve the specific objectives (Figure 1.4). Spatial and temporal patterns of malaria are presented in chapter 4. High risk areas and socio-ecological drivers of malaria are examined in chapter 5. Whether the microscopic surveillance indicator - slide positivity rate (SPR) can estimate the incidence of malaria and can be used to validate the malaria surveillance systems in China is explored in chapter 6.

Chapter 4 specifically focuses on visualising and analysing the spatial and temporal patterns of malaria mortality in Yunnan Province, China using GIS tools and SaTScan method, which was published in the *American Journal of Tropical Medicine and Hygiene*.

Chapter 5 identifies the high risk areas of malaria incidence in Yunnan Province and further assesses the effects of socio-ecological variables on weekly malaria cases in the identified primary cluster area. The manuscript is under submission.

Chapter 6 examines the role of slide positivity rate (SPR) in malaria transmission, which was published in the *Malaria Journal*.

Chapter 7 summaries the key findings from chapters 4-6 and also outlines conclusions in relation to the overall aim of the study. This chapter further discusses the strengths and limitations of the study, public health implications and future research directions.

Tables and figures are provided in the text to facilitate reading and understanding. The references are presented at the end of each chapter. A complete list of bibliography (including references cited in the individual manuscripts) is provided at the end of the thesis.

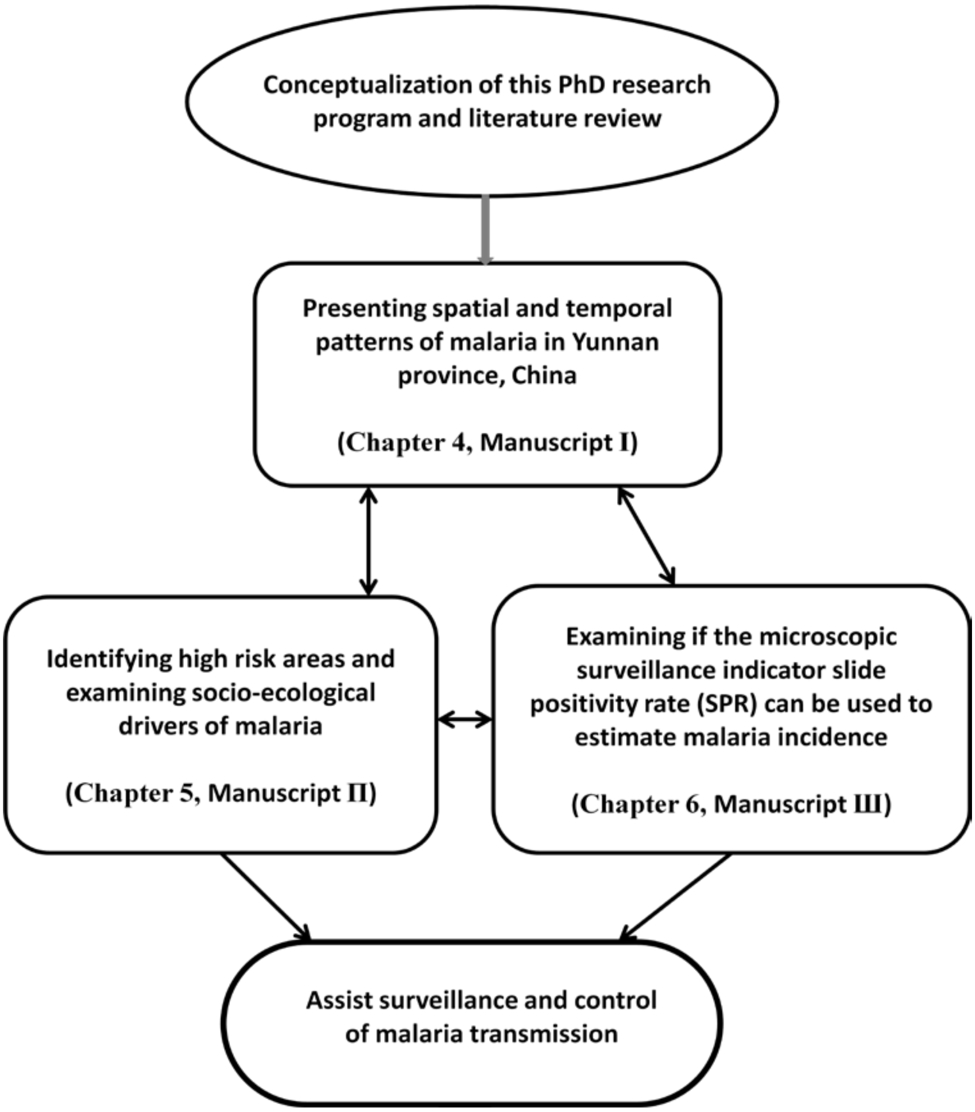


Figure 1.4 Flowchart of the thesis manuscripts

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Chapter 2: **Literature Review**

2.1 Introduction

The past decades have witnessed the geographic shrink of malaria endemic areas from 178 countries in the first half of the 20th century to 104 countries in 2012, in which 99 countries were endemic and 5 countries were in the prevention and reintroduction stage. There was an estimated 50% of the world's population living in malaria endemic areas (Feachem *et al.* 2010b). Additionally, malaria has emerged as a significant public health issue in some regions, such as, east Africa highland areas (Hay *et al.* 2002). The emergence of malaria may be related to a number of factors including socio-ecological variation, increased human movement, land clearance, urbanization and climate change (Al-Taiar *et al.* 2009; Berrang-Ford *et al.* 2009; Craig et al. 2007; Hay *et al.* 2005; Reiter 2001; Tanser *et al.* 2003). Recently, GIS and spatial analysis techniques are increasingly been used in mosquito-borne diseases including malaria. This review begins with a description of GIS functions and its applications in malaria transmission. After that, the potential risk factors are explored including temperature, rainfall, relative humidity, seasonality, lag effect, human movement and international travel, land clearance and urbanization and socio-economic status. Finally, the knowledge gaps in this area are discussed.

2.1.1 Review of the literature

A literature search was conducted with the electronic databases including PubMed, Scopus, ScienceDirect and Web of Science. The search was limited to peer-reviewed journal articles published in English from January 1993 through April 2013. Majority of relevant articles were retrieved using U.S. National Library of Medicine's Medical Subject Headings (MeSH terms) and keywords: "malaria", "geographic information system", "GIS", "spati*-temporal", "space-time", "risk factor", "climat*", "environment*", "ecologic*", and "socio-economic*". Additional relevant publications were indentified through the reference list of publications. Research reports from international and local government organisations were also included in this review. The objective of this review is to understand the impact of social-environmental determinants on malaria transmission and the applications of GIS and spatial analysis in malaria control and prevention activities.

2.2 GIS capabilities and applications in malaria surveillance and control

2.2.1 GIS capabilities

GIS is described as "an organised collection of computer hardware, software, geographical data, and personnel designed to efficiently capture, store, update, manipulate, analyse and display all forms of geographically referenced data" (Rhind *et al.* 1990). It emphasises the importance of map processing, databases and spatial analysis (Maguire *et al.* 1991) by "providing the means to store, share, analyse, and visualise real-time and archived spatial data" (Richardson *et al.* 2013).

The functional capabilities of GIS are classified into data capture, storage, records and display according to GIS definition and combined the elements necessary for problem solving and analysis (Clarke *et al.* 1996). The capture and storage functions of GIS allow different sources of dataset to be integrated and analysed. GIS is also able to provide functions for spatial analysis, information query, modelling, and accurate mapping with visual, efficient spatial, temporal and thematic data (Pfeiffer *et al.* 2008). Visualisation provides maps to display spatial patterns, which are useful for more complex analyses. The GIS spatial analysis is considered to be the most important and powerful function. The spatial relationship is the principal focus for disease prevention and control, especially in spatial epidemiology. Both Clarke (1996) and Pfeiffer (2008) grouped spatial analysis functions into three general types: visualisation, exploratory data analysis and model building.

2.2.2 The applications of GIS in malaria surveillance and control

2.2.2.1 Malaria surveillance

Surveillance systems are important for public health as it can provide timely support for decision making of endemic diseases, identification of epidemic outbreaks and evaluation of health programs (Nobre *et al.*1997). Oaks *et al.* (1991) recommended that “malaria surveillance may be the most important first step for endemic countries hoping to understand and manage their malaria problem”.

Some successful examples using GIS-based surveillance systems to analyse data, provide information for decision making and surveillance-response strategy planning in malaria control and elimination programmes were reported. For instance, in Israel (Kitron *et al.* 1994), a national malaria surveillance system was established using GIS techniques to detect the breeding sites of vector mosquitoes and imported malaria cases. This system contained both epidemiological and entomological data which can be integrated to create visual maps, calculate distances between population centres and breeding sites, and assist in identifying the potential infectious sources (probable human population), vector mosquitoes (five types of

Anopheles) and breeding sites promptly. This GIS-based surveillance system ensures an alert of localized malaria outbreak, by providing risk assessment of vectorial capacity and flight range of each Anopheles species.

Nobre (1997) described how GIS was used to support public health surveillance and epidemiological investigations. This GIS-based surveillance system presents a simple system to create and display maps, and to perform exploratory analysis on identifying potential risk areas, time trends and comparative analysis. This study provided an efficient way by applying GIS techniques for public health authorities to support malaria control activities in malaria surveillance systems.

Recently, a GIS-based spatial decision support system (SDSS) has been developed in Solomon Islands and Vanuatu (Kelly *et al.* 2013). The application of this geospatial surveillance-response system provided local health authorities to identify and map the distribution of confirmed malaria cases, classify active transmission foci, and guide targeted responses in these Pacific Island countries.

The Atlas of the Asia Pacific Malaria Elimination Network (APMEN) displayed the geographic distribution of malaria in the 11 countries of the network to assist malaria eliminating partner countries with clear pictures of malaria distribution. GIS as a useful tool is increasingly applied in malaria surveillance to develop response strategies, predict outbreaks and prevent disease reintroduction (Hightower *et al.* 1998; Booman *et al.* 2000; Martin *et al.* 2002; Hassan *et al.* 2003; Srivastava *et al.* 2003; Hanafi-Bojd *et al.* 2012).

2.2.2.2 Spatial and temporal modelling

GIS and spatial and temporal modelling methods are increasingly used in MBD surveillance and risk management, which can help us to understand the distribution of disease in space and time. For example, GIS and spatio-temporal modelling have long been applied to display and model the spatial variation of malaria (Clarke *et al.* 1996); define the time and space distribution (Craig *et al.* 1999; Brooker *et al.* 2004; Coulibaly *et al.* 2013), seasonality (Hay *et al.* 1998b; Tanser *et al.* 2003), morbidity and mortality (Snow et al. 1999); and identify high risk locations of disease transmission (Beck *et al.* 1994; Ernst *et al.* 2006; Srivastava *et al.* 2009; Wen *et al.* 2011; Bi *et al.* 2013).

To evaluate malaria control and elimination strategies, GIS techniques have been adopted to visualise malaria risk and assess time-space distribution of malaria in Mali, West Africa (Coulibaly *et al.* 2013). This study found that *P. falciparum* occurrence was clearly temporally related to the rain season and persisted up to the beginning of the dry season, and two “hotspots” of malaria transmission were identified at a town level. These findings provided assistance for the local implementation of targeted interventions.

A GIS-based spatial composite model has been used to predict the transmission tendency of malaria in China (Yang *et al.* 2002). The spatial analyst extension function of ArcView was used to create maps of multifactors including total growing degree days (TGDD), precipitation and relative humidity. The results of this study found that the high risk areas of malaria transmission were consistent with the previous reports in China.

Lin *et al*. (2009) found that an endemic area of *falciparum* malaria remained in two southern provinces in China, i.e. Yunnan and Hainan. GIS and spatio-temporal methods were used to identify stable transmission of *P. falciparum* happened in the border region of Yunnan and the hilly-forested south of Hainan. The age and gender distribution in the endemic area was characterized by the predominance of adult male cases. GIS tools were also applied in Yunnan Province to examine the spatio-temporal variation of malaria incidence (Clements *et al.* 2009) and to identify spatial and temporal clusters of both *P. vivax* and *P. falciparum* (Hui *et al.* 2009). In Hainan Province, to further support public health planning and resource allocation in the future malaria programmes, Wen et al. (2011) conducted a study to explore the temporal and spatial variation of malaria epidemic in a hyper-endemic area at a village level. Since 2000, because of resurgence of malaria in China, Anhui Province was the most seriously affected area in the country, with the highest number of malaria cases in 2005 (Zhou *et al.* 2006). Zhang and colleagues (2008) applied GIS-based spatial techniques to quantify spatial distribution and population at high risk of malaria incidence at a county level in Hainan. They found that 10 and 24 counties, which identified as spatial cluster areas, were at increased risk for malaria with the maximum spatial cluster sizes at < 50% and < 25% of the total population, respectively.

2.2.2.3 Mosquito vector control

GIS spatial modelling capabilities were integrated with remote sensing (RS), which could extend not only monitoring the spatial and temporal patterns of infectious diseases but increasing the capabilities for disease surveillance and control, and particularly identifying and mapping habitats of mosquito vectors (Beck *et al.* 2000).

The first investigation for larval habitat mapping was the use of colour-infrared (CIR) aerial photography to identify the larval habitat of the nuisance saltmarsh mosquito by scientists from National Aeronautics and Space Administration (NASA) in 1971 (Hay *et al.* 2000).

A study by Pope et al. (1994) provided an example to integrate RS, GIS and field research to predict *Anopheline* mosquito population dynamics in the Pacific coastal plain of Chiapas, Mexico. The Landsat Thematic Mapper (i.e. TM-based map) and GIS techniques were used to predict differences in *Anopheline* production at two malaria endemic villages. The TM data was integrated in a GIS format to detect correlations between *Anopheline* habitat-types and land cover units, and to measure the larval habitats in low, medium and high producing types. The results provided valuable information on where to focus malaria control efforts in the two villages. For example, when resources are limited, high priority should be given to larval habitats in the high and medium *Anopheline* producing land cover units.

GIS-based spatial modelling approach was used to assess the spatial patterns of malaria mosquito vector breeding habitats in Thailand (Sithiprasasna *et al.* 2003). In this study, Global Positioning System (GPS) was applied to locate accurately each field observed breeding habitat, and a 30-m spatial resolution Digital Elevation Model (DEM) was produced. In the spatial model, the surface slope and wetness were considered and derived to identify the extent and spatial pattern of potential mosquito breeding habitats. Positive associations were found between slope and wetness and the abundance of four major malaria vectors, which allow real-time monitoring and possible forecasting to be given to support field mosquito vector control in this country.

An increasing number of studies have used the spatial modelling capability of GIS and RS techniques to detect and assess malaria risk (Ceccato *et al.* 2005); define the distribution (Craig *et al.* 1999; Brooker *et al.* 2004), high risk locations (Beck *et al.* 1994;Ernst *et al.* 2006; Srivastava *et al.* 2009), transmission intensity (Patz *et al.* 1998; Snow *et al.* 1998; Rogers *et al.* 2002), and seasonality (Hay *et al.* 1998b;Tanser *et al.* 2003) of malaria; to estimate population exposure, morbidity (Clements *et al.* 2009) and mortality (Snow *et al.* 1999), and to analyse (Hay *et al.* 2002) and project the effects of climate change on malaria transmission (Lindsay *et al.* 1998;Tanser *et al.* 2003).

2.3 Potential determinants of malaria transmission

2.3.1 Role of climatic factors

Climatic factors are important determinants of malaria transmission (Berrang-Ford *et al.* 2009). Malaria is identified to be the most prominent “climate sensitive disease” (Githeko *et al.* 2000) since malaria occurrence is related to distribution and abundance of vector mosquitoes which are influenced by climatic factors including temperature, rainfall, relative humidity and seasonality (Hamad *et al.* 2002). The spatial and seasonal distribution of malaria is largely determined by climate (Tanser *et al.* 2003). Various studies demonstrate that climatic factors are important determinants of the transmission of malaria.

2.3.1.1 Temperature

Temperature plays a crucial role in the transmission cycle of *Plasmodium* parasite and mosquito survival (Brooker *et al.* 2004; Mordecai *et al.* 2013). Temperature has an important effect on the life cycle of *Plasmodium* parasite (Blanford *et al.* 2013). The length of the parasite cycle depends on the temperature and other climatic factors (Martens *et al.* 1995). Parasite development in the mosquito is considered to cease at 16 ℃, and transmission below 18 ℃ is unlikely and unstable. However, temperature above 22 ℃ is suitable for stable transmission (Craig *et al.* 1999). Temperature also influences mosquito survival. The optimum temperature for mosquito survival is between 20 ℃ and 25 ℃ (Martens *et al.* 1995), and for the transmission of malaria is at 25 ℃ (Mordecai *et al.* 2013). It is also found that the most suitable temperature for the rapid expansion of a malaria mosquito population is in the range of 20-30 ℃. Within certain ranges, rising temperature shortens the interval between blood meals and increases biting rate of mosquito, and accelerates development of parasite, thus increases epidemic potential (Martens *et al.* 1995). A high temperature should increase the likelihood of transmission since it shortens the incubation period (Reiter 2001). Studies have showed that a very high temperature (around 40-42 ℃) will cause death of both mosquito (Craig *et al.* 1999; Dale *et al.* 2005) and parasite (Dale *et al.* 2005). Daily survival rate of mosquitoes is zero at 40

℃ (Craig *et al.* 1999). While, low temperatures can also reduce mosquito abundance because of the long larval duration (Dale *et al.* 2005; Kleinschmidt *et al.* 2001). Therefore, temperature is considered to be a key determinant of malaria transmission (Gething *et al*. 2011).

Some researchers (Martens *et al.* 1995; Tanser *et al.* 2003; Alonso *et al*. 2011) examined and quantified the association between temperature and malaria transmission. Kleinschmidt *et al.* (2001) found average daily maximum temperature has a large effect on malaria incidence._They also predicted that even a small difference in climate can have marked effects on the intensity of malaria transmission, even in controlled areas with malaria, for many years. A strong positive correlation was found between minimum temperatures and monthly malaria incidence in Ethiopian by Tulu (1996). Similarly in Zimbabwe, temperature has a strong effect on the severity of malaria incidence and is a predictor of severe malaria years (Freeman *et al.* 1996). Alonso *et al*. (2011) supported that the deterioration of malaria was affected by warmer temperature in East African highland.

2.3.1.2 Rainfall

Rainfall plays a principle role in malaria transmission and burden of this disease (Kovats *et al.* 2001). The influence of rainfall on malaria transmission is complex. Rainfall can increase breeding sites and create ground pools. Evaporation of pools keeps relative humidity at a high level which prolongs longevity of vector mosquitoes. In addition, heavy rainfall or storms may destroy existing breeding places, interrupt the development of mosquito eggs or larvae, or simply flush the eggs or larvae out of the pools (Tian *et al.* 2008). For vector mosquitoes living in floating water, heavy rain may flush larvae away, while for those in stationary water, heavy rain followed by drought can enlarge their temporary habitats and accelerate the mosquito population (Bureau of Endemic diseases Control of People's Republic of China. 1998).

Analysis of rainfall patterns has been used to predict malaria epidemics. The severity of the annual outbreaks is influenced by rainfall in Sudan (Hamad *et al.* 2002). Rainfall initiated malaria epidemic in highland of Africa as well. This was supported by Lindblade *et al.* (1999) and Kilian *et al.* (1999). They found that excessive rainfall resulted from ENSO during 1997-1998 was responsible for malaria epidemics and were positively correlated with vector mosquito density in Uganda during 1997-1998 (Lindblade *et al.* 1999). Research carried out by Mabaso *et al.* (2006) also showed annual mean rainfall, temperature and vapour pressure are strong positive predictors of increased annual malaria incidence in Zimbabwe. Bhattacharya *et al.* (2006) found rainfall in the previous October coincided with increase in malaria incidence in the subsequent year and rainfall in May wiped out malaria incidence in south-western parts of India. Clements *et al.* (2009) indicated that rainfall plays an important role in driving spatio-temporal patterns of malaria incidence in Yunnan Province, China. It is evident that rainfall is generally a significant factor which has a close relation with malaria epidemics (Dale *et al.* 2005).

2.3.1.3 Relative humidity

Relative humidity (RH) seems to have an indirect effect on the development of parasite but may affect the activity and survival of *Anopheline* mosquitoes (Dale *et al.* 2005). The optimal survival condition for *Anopheline* mosquitoes for average RH is above 60% with temperature between 20 ℃ and 30 ℃ (Bureau of Endemic Diseases Control of P.R. China. 1998). If the average RH is below 60% (Bureau of

Endemic diseases Control of People's Republic of China 1998) or above 80% (Bhattacharya *et al.* 2006), the life span of the mosquito is shortened. If the average RH is below 52%, mosquitoes will cease blood biting activity (Bureau of Endemic diseases Control of People's Republic of China 1998), the mature mosquito survival will be considerably reduced by the low humidity (Keiser *et al.* 2002), so that there is no malaria transmission (Dale *et al.* 2005).

A number of studies were conducted to better understand the effects of RH on malaria transmission. A study conducted in Kenya demonstrated that climatic factors, particularly moisture index and temperature, strongly affected the distribution and abundance of malaria vectors. They found moisture index which calculated as the ratio of precipitation to potential evapotranspiration was the only variable significantly associated with relative abundance of *An. gambiae*, a predominant species that transmits *P. falciparum* in Africa (Minakawa *et al.* 2002).

Another analysis examined if climatologic variables including humidity, temperature and rainfall affected the transmission of *P.falciparum* in Northwest Frontier province of Pakistan (NWFP). The average humidity showed a significant increase and appeared to be important for *P.falciparum* transmission between 1950 and 1993. At the end of the transmission season, humidity in December was correlated significantly with *P.falciparum* infections. Relative humidity appears to be a principal factor for *P. falciparum in* NWFP, and has also been suggested for epidemics in Sind Province, Pakistan (Bouma *et al.* 1996).

In the United States, several outbreaks of locally acquired malaria occurred in New Jersey, New York City and Houston in the early 1990s, which created concern amongst both the general public and academics. The result of investigations found the factors that contributed to these outbreaks included greater humidity and hotter temperature, which may increase *Anopheline* survival and decrease the duration of the sporogonic cycle (Zucker *et al.* 1996). A similar result was found in eastern Sudan (Hamad *et al.* 2002). *An. arabiensis* reappeared in June as humidity rose with the onset of rain.

2.3.1.4 Seasonality

Seasonality is a key component of climate (Reiter 2001). Climate change will influence seasonal transmission and potential incidence of malaria (McMicheal *et al.* 2006). There are seasonal differences on malaria transmission which are largely driven by annual ranges of climatic conditions such as rainfall and temperature (Hay *et al.* 2000). Areas with seasonality of transmission are defined to seasonal and stable in Africa. In terms of transmission season, in seasonal regions, monthly moving mean temperature and rainfall had to be 22 °C and 60 mm, respectively, and here had to be at least one month of highly suitable conditions (> 22 °C and > 80 mm). In the stable regions, however, monthly moving averages only had to be 19.5 °C for temperature, but 80 mm for rainfall, and no highly suitable month had to occur (Adjuik *et al.* 1998).

'Malaria seasons' is recognised by most clinical staff and experts working in malaria endemic areas. Hay *et al.* (1998a) studied seasonal fluctuations in clinical malaria and showed different seasonal patterns of malaria cases. They revealed annual malaria cases with peaks around January and July following the short and long rainy seasons respectively in Kilifi North Kenya. They also predicted malaria seasonality. A significant correlation between the temporal changes of meteorological and vegetation variables and relative changes of severe malaria cases were demonstrated. The malaria seasonality maps were then created for Kenya.

A seasonality model was also produced to project changes in malaria transmission patterns in different climate scenarios during the period of 2010-2099 by Tanser *et al.* (2003). They applied a spatio-temporally validated model of malaria transmission based on climatic variables to estimate that by 2100, in South Africa, person-months of exposure will increase by more than 100%. This effect would result from the rises in malaria distribution and seasonal lengths.

Abellana *et al.* (2008) studied the seasonal effect on the spatial distribution of malaria transmission based on spatio-seasonal model in Mozambique. Malaria incidence was associated with period and climate season. Malaria presented a clear spatial pattern with a highest incidence during the wet season. Tian *et al.* (2008) found seasonality was apparent in a tropical rain forest area in China. In this study, besides the major incidence peak in the rainy season (May-October), there was also a minor peak in the dry-cool season (November-February). A clear seasonality of malaria incidence had been demonstrated in Thailand-Myanmar border, with two peaks (May-July, October-November) which were closely associated with the patterns of rainfall (Zhou *et al.* 2005). The seasonal peaks were most distinct in foreigner malaria cases. Different seasonal patterns were found in the study of Mabaso *et al.* (2005) in Zimbabwe. They described the intensity of seasonal transmission was lowest in the whole country (July-December) and was highest in the north western Zimbabwe (February-May) and peaking in April.

Seasonal information can support and allow the development of malaria control calendars and may also help health services concentrate on control activities (Connor *et al.* 2006).

The factors determining the distribution and seversity of malaria are diverse and complex. However, climatic predictors can be considered the major determinants. Temperature and rainfall limit malaria to the warm, humid regions, where the mosquitoes and parasites can breed and develop with different seasonal patterns, and thus transmission can occur (Adjuik *et al.* 1998).

2.3.2 Role of non-climatic factors

Besides climatic influences on malaria transmission, non-climatic factors such as human activities, population movement, socioeconomic status, vector control programs and environmental changes also affect the spread of this disease (Githeko *et al.* 2000; Lindsay *et al.* 1998; Reiter 2001). These non-climatic effects are demonstrated by a number of studies as illustrated below.

2.3.2.1 Human movement and international travel

The increasing trends of human movement and international travel will likely contribute to the increase of malaria transmission (Craig *et al.* 2004; Al-Taiar *et al.* 2009; Berrang-Ford *et al.* 2009). A study showed that human movement across the border between South Africa and Mozambique has been attributed to the highest malaria incidence in the local area. In 1996, 58% of people across the border were infected by malaria (Craig *et al.* 2004). A strong association between the history of travel and malaria has also been identified in Yemen, Gambia and Colombia (Al-

Taiar *et al.* 2009; Koram *et al.* 1995; Osorio *et al.* 2004). Al-Taiar *et al.* (2009) and Koram *et al.* (1995) reported that the risk of malaria infection was higher in travelers from urban and semi-urban to rural areas. Osorio *et al.* (2004) investigated the risk of travelling to endemic areas. The results demonstrated that travelling outside the urban area was the strongest risk factor for malaria in the town of Quibdo, Columbia. Residents who travelled outside the town had a higher risk than local residents who did not travel. The results provided useful information to highlight more effective malaria control measures for targeting a mobile population.

Increasing international travel and immigration might be responsible for the increase of imported malaria to Canada (Berrang-Ford *et al.* 2009). International travel and immigration were identified to introduce parasites into the local population and were associated with two most significant outbreaks in Canada, i.e. in 1995-1997 and 2001-2002.

International travel can also increase the risk of malaria transmission in China. In recent years, increasing trends of overseas of labor services to Myanmar and African countries (Zhou *et al.* 2009), international trade and tourism to the Southeast Asia countries (Hu *et al.* 1998) have contributed to the expansion of malaria transmission in China. In 2008, all malaria deaths were from overseas imported cases in China (Zhou *et al.* 2009).

Huge population movement is quite common in China which increases the risk of malaria transmission (Zhou *et al.* 2009). Imported malaria cases from neighbouring countries are a serious problem (Zhen *et al.* 2003). In Tengchong county sharing a border with Myanmar, 4,119 malaria cases were reported during the period of 1997-2001, and more than 95% of these cases were imported. The frequent cross-border movement might have contributed to malaria transmission since regular register records showed that 127,893 foreigners entered Tengchong from Myanmar and 299,320 Chinese visited Myanmar, during the same period (Yang *et al.* 2003). Consequently, cross-border human movement creates constant potential of malaria importation (Feachem *et al.* 2010a).

Zhu *et al.* (1994) and Shi *et al.* (2004) reported war-related human movement and consequently an increase of malaria transmission along Myanmar-China border. Nearly 8,000 refugees entered Longchuan county from Myanmar in 1987. From blood smears in 1,192 refugees, 397 persons were positive parasite. A parasite rate was 33.3% (397/1192), and among them, *P.f* accounted for 82%. Three malaria outbreaks were reported in this county from 1987 to 1992 because more than 40 thousands refugees crossed the board to avoid civil wars in Myanmar.

Therefore, the movement of infected people from areas where malaria is endemic to areas with low rates or malaria-free can lead to resurgence of disease (Dale *et al.* 2005). Conversely, non-immune or low immune people are prone to be infected by malaria if they travel or move to malaria endemic regions (Reiter 2001).

2.3.2.2 Land clearance and urbanization

The change of land use and land cover may influence the distribution and abundance of mosquitoes (Bureau of Endemic diseases Control of People's Republic of China. 1998). Clearance of forest for the purpose of crops growth may create abundant new habitats for mosquitoes (Lindsay *et al.* 1998; Reiter 2001). Deforestation has been one of the reasons for the increase of malaria in Usambara, Tanzania (Lindsay *et al.* 1998). Irrigation for crop cultivation, particularly for rice fields, can affect malaria transmission (Lindsay *et al.* 1998). Interestingly, a study in Burundi (Marimbu *et al.* 1993, cited in Lindsay *et al.* 1998) investigated that a malaria epidemic was related to the expansion of local rice fields and development of fish ponds. On the contrary, Chen *et al.* (2002) reported that with the introduction of new innovation of irrigation system in rural areas in Sichuan since the 1970s, farmers changed their traditional way of growing rice, irrigation schemes and enlarged the usage of insecticide. The mosquito density dramatically decreased by 71% in human houses and 87% in cattle houses. These strategies sharply reduced breeding sites of vector mosquito in this region. One plausible explanation (Ijumba *et al.* 2001) for this is that the introduction of irrigation scheme for rice cultivation results in increasing income in local communities, which often has better access to improved healthcare and greater use of protective methods. This was supported by another study (Ijumba *et al.* 2002) which found that irrigated crop production was associated with less malaria than transitional agriculture practices in Tanzania.

Rapid urbanization has apparent effects on malaria risk by changing the behavior and breeding sites of mosquitoes (Hay *et al.* 2005; Reiter 2001). A study from Sub-Saharan Africa (Robert *et al.* 2003) examined the relationship between annual entomologic inoculation rates (EIR) and the level of urbanisation. The results showed that EIRs decreased with 167.7/year in rural areas, 45.8/year in periurban and 7.1/year in cities. Urbanization level has a remarkable impact on malaria transmission in this region. Hay *et al.* (2005) showed a collapse of malaria transmission with growth of urbanization and population from 1930s to 1960s in Nairobi, Africa. This is because people living in urban areas have a higher quality of houses and can access better health facilities. Consequently, urban people suffer less morbidity and mortality from malaria than rural residents.

2.3.2.3 Socio-economic status

Socioeconomic factors may directly or indirectly affect malaria transmission (Temel 2004). Malaria transmission is largely affected by socioeconomic conditions (Brooker *et al.* 2004; McMichael *et al.* 2006). Failure of consideration of socioeconomic effects might be responsible for the failure of malaria control programs (Al-Taiar *et al.* 2009). Dale *et al.* (2005) found that low-middle income and lower education levels were significantly associated with malaria in Indonesia. A study in Thailand showed a longer residence duration (adjusted OR = 0.36, 95% CI) and the use of anti-malarial self-medication (adjusted OR = 0.08, 95% CI) were significantly associated with protection from severe malaria (Nacher *et al.* 2001). Koram *et al.* (1995) also found that children living in poor quality housing and crowded dwellings were infected with malaria more frequently than other children living in better housing conditions in periurban areas in Gambia. Ijumba *et al.* (2001) demonstrated that the disappearance of malaria in some areas of Europe was associated with economic development and there is enough historical evidence to support that economic development has a positive impact on health.

2.3.2.4 Other potential risk factors

Many other factors might potentially influence malaria transmission. Dale and colleagues (2005) found that outdoor activities are a higher risk behavior as mosquitoes are most active between dusk and dawn. The highest risk of malaria transmission is where mosquito host seeking behavior coincides with places and times of human presence (Ndoen *et al.* 2011). The use of bednets, repellents, wearing long sleeve shirts and long pants all reduce the risk of malaria. Housing type and quality can directly influence malaria incidence (Gaunawardena *et al.* 1998). Building houses close to water sources and the forest edge facilitated the spread of malaria (Ghebreyesus *et al.* 2000; Gaunawardena *et al.* 1998). Deterioration in health care systems and facilities appears to increase malaria transmission (Lindsay *et al.* 1998; Reiter 2001). The rapid increase of both anti-malarial drug resistance and insecticide resistance is a major problem which restrains the control of malaria (WHO 2009). Therefore, the WHO introduced two powerful and broadly used intervention tools, i.e. insecticide-treated nets (ITN) and indoor residual spraying (IRS) to reduce the intensity of local malaria transmission. Natural disasters are considered to accelerate the spread of malaria infection (Reiter 2001). People working as farmers at working ages are more likely to catch malaria than those who are not farmers and not at the working ages in Indonesia (Dale *et al.* 2005). Altitude has been considered to limit malaria incidence, especially linked with temperature (Brooker *et al.* 2004; Craig *et al.* 2007; Hay *et al.* 2000). The altitude ranged 0-800 meters is considered to be a significant risk factor for malaria in Iran (Hanafi-Bojd *et al.* 2012). ENSO is also considered to associate with malaria outbreaks and increased malaria epidemic risk (Kovats *et al.* 2003; Lindblade *et al.* 1999)

It is evident that risk factors of malaria transmission are complex and vary with space and time. To prevent and control the spread of malaria infection, non-climatic determinants should not be ignored. A combination of both climatic and non-climatic risk factors of malaria transmission should be considered together at local, regional and national levels. The most relevant risk factors of malaria transmission in literatures are shown in Figure 2.1. The socio-ecological determinants of malaria transmission which will be collected in this research are also demonstrated in the figure since these factors are considered as key drivers of malaria transmission.

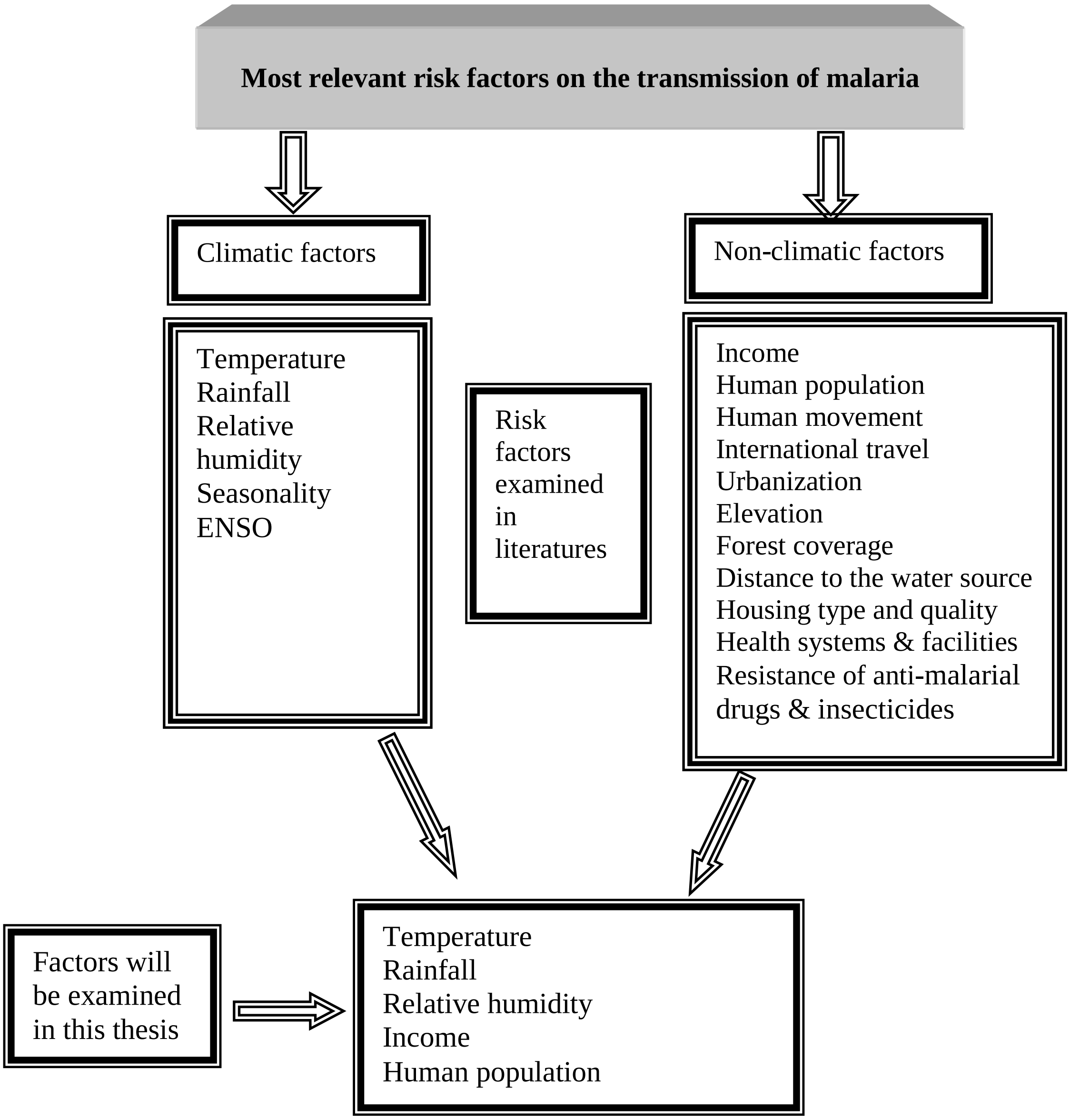

Figure 2.1 Flowchart of most relevant risk factors of malaria transmission

2.4 Spatio-temporal analysis of risk factors of malaria transmission

Among three basic elements (person, place and time) of disease outbreak investigations, both space (geography) and time are two key components (Moore *et al.* 1999). Geography can give valuable clues to understand social-environmental and behavior interaction with health and disease. Spatial patterns of diseases are not only important but intricate and complex and the spatial distribution of diseases can uncover important information of disease transmission (Zhou *et al.* 2009). Intensity and timing of malaria transmission is essential for local epidemics and temporal trends are governed by seasonal and inter-annual variation (Mabaso *et al.* 2006). For instance, malaria transmission is driven by a bunch of risk factors including environmental factors, biological and anthropogenic factors (Ceccato *et al.* 2005). All of these factors may have spatial and temporal variations influencing the extension and intensity of malaria transmission through different geographic regions.

To better understand spatial and temporal changes of malaria transmission, recently, some spatial analytical methods have been adopted to assess the association between social-environmental determinants and malaria transmission. For example, GIS is a supportive tool that can be used to better understand the spatial variation of disease and its relationship to socio-environmental factors and the health care system (Clarke *et al.* 1996; Tanser *et al.* 2002). GIS spatial analytical tools supply epidemiologists with visualisation, management, analysis and integration of various data (Zhou *et al.* 2009). RS is a data source which can provide temperature, rainfall, land cover, vegetation, topography and other environmental parameters in different space and time resolutions, and it has become increasingly important for epidemiologic and public health research (Bergquist 2001; Graham *et al.* 2004). The advantages of GIS/RS techniques provide a spatial analysis platform and link different data sources together to produce high-resolution risk maps and perform risk factor analyses to support malaria identification, monitoring and surveillance (Hay *et al.* 2000; Zhou *et al.* 2009). By using these approaches, researches have been conducted to assess risk factors of malaria transmission over space and time world widely.

2.4.1 Malaria mapping

GIS mapping has contributed to the development of spatial epidemiology of malaria (Saxena *et al.* 2009). Some successful examples using GIS techniques to create global, continental, national and local maps on endemic malaria were reported. For example, global risk maps of malaria endemic have been generated to quantify the anthropogenic impact on the geographical distribution of malaria in the 20^{th} century by Hay *et al.* (2004). From these distribution maps of malaria risk factors at different intervals subdivided by malaria endemicity classes, the global trends and population at risk of malaria over the last century (1900-2002) were clearly visualized. Snow *et al.* (2005) combined multiple sources including epidemiological, geographical and demographic data to estimate global clinical episodes caused by *P.falciparum.* The distribution of malaria mosquitoes, breeding settings and potential population is important to develop effective strategies for malaria control and prevention. Kitron *et al.* (1994) mapped two types of data: the breeding sites of vector mosquitoes which transmit malaria and the imported malaria cases. These visualisation maps help to analyse these two types of data to identify the potential infectious sources, vector mosquitoes (five types of anopheles) and breeding sites promptly. Maps from this GIS-based malaria surveillance system provide valuable information on malaria vector monitoring and potential population surveillance in Israel. To better understand seasonal fluctuations in clinical malaria, maps of seasonal clinical cases were created in Kenya (Hay *et al.* 1998). The malaria seasonality map based on vegetation index (NDVI) was perfectly matched with a previous existing map (in 1959) of malaria transmission for this country.

Two studies (Gemperli *et al.* 2006; Kleinschmidt *et al.* 2001) showed maps of malaria transmission with similar prevalence patterns in West Africa, especially for regions with the high malaria prevalence. From risk maps and spatial analyses, it suggested that seasonal differences could not be ignored in the African continent. GIS-based spatial statistical techniques were used to detect the spatial distribution of malaria cases in re-emerged epidemic areas and produced maps to display crude incidence, excess hazard and spatial smoothed incidence in the study of Anhui Province, China (Zhang *et al.* 2008). GIS mapping was also used to display the geographical pattern of malaria incidence in Yunnan Province, China (Hu *et al.* 1998). GIS maps showed that annual malaria incidence rates were higher in counties in border and along Yuan River than other counties in Yunnan.

As a good communication tool, mapping provides a supportive function for monitoring malaria in the distribution, epidemic trends and prediction of seasons over a geographic area (Kitron *et al.* 1994; Tsoi 2007). However, maps are not good at presenting an association between response and explanatory variables (Zhou *et al.* 2009). To further understand the complex nature of the spatial distribution, spatial analytical techniques are needed.

2.4.2 Cluster detection – application of spatial scan statistic

Clustering of a disease can be related to a number of reasons. It is fundamentally important to investigate possible disease clustering in epidemiology (Pfeiffer *et al.* 2008). In a variety of cluster detection methods, a spatial scan statistic is commonly used to test whether any clusters can be detected or if point process is purely randomly distributed (Kulldorff 1997). This scan statistic approach has been widely applied to detect clustering regions and periods in a range of chronic and infectious diseases such as breast cancer (Kulldorff *et al.* 1997), brain cancer (Kulldorff *et al.* 1998), prostate cancer (Klassen et al. 2005), West Nile Virus (Mostashari *et al.* 2003), filariasis (Washington *et al.* 2004), hemorrhagic fever (Fang *et al.* 2006), schistosomiasis (Zhang *et al.* 2008), Dengue (Morrison *et al.* 1998) and malaria (Brooker *et al.* 2004; Coleman *et al.* 2009; Gaudart *et al.* 2006; Haque *et al.* 2009; Hui *et al.* 2009; Yeshiwondim *et al.* 2009; Zhang *et al.* 2009; Wen *et al.* 2011; Bi *et al.* 2013).

Western Kenya experienced a malaria outbreak during May-July 2002. Brooker *et al.* (2004) carried out a study to identify spatial clusters of malaria cases through the spatial scan statistic and explore potential risk factors in this highland region. They identified locations where malaria risk was higher and compared malaria cases identified inside and outside a spatial cluster throughout epidemic areas. With the improved understanding of the spatial clusters, the results of the spatial clustering provided further insights into the assessment of risk factors for malaria in the study area.

In a study by Hui *et al.* (2009), spatial clusters of both *P. falciparum* and *P.vivax* were identified along border areas at a county level in Yunnan Province, China. They found that the high risk areas of malaria transmission were adjacent to neighboring countries-Myanmar, Laos and Yuanjiang River Basin. A temporal cluster was also identified which showed seasonal fluctuations in malaria incidence. Peak times of malaria took place in summer and autumn with a single peak during 1995-2000 and bimodal through 2001-2005. In South Africa, both space-time clusters were detected at a town level in a low malaria transmission area - Mpumalanga Province during

2002-2005 (Coleman *et al.* 2009). Five space-clusters and two space-time clusters were detected which were coincident with outbreaks reported in local towns. It was suggested that the exploration of malaria clusters can assist outbreak identification and disease control planning.

The identification of areas and times of malaria clusters may provide important information for health authorities on where and when to implement anti-malaria measures properly and promptly (Hui *et al.* 2009), whereas the results from cluster analysis can only provide general information of the disease clusters in terms of space and time (Brooker *et al.* 2004). To understand the association between risk factors and malaria transmission (in space and in time), and to investigate reasons for spatial clustering, other analytic techniques are necessary.

2.4.3 Spatial and temporal analyses

To investigate risk factors of malaria incidence at a district level in Zimbabwe (Mabaso *et al.* 2006), Bayesian negative binomial models were conducted to explore the relationship between climatic variables and malaria incidence. Their study confirmed inter-annual variation of malaria transmission with the highest risk years were during the most wet periods and the lowest risk years over the severe drought periods in Zimbabwe. This seasonal variation was mainly driven by climatic factors. Seasonal effects on the spatial distribution of the malaria incidence were also explored in Mozambique (Abellana *et al.* 2008). Hierarchical Bayesian models were used to model the malaria incidence which had an association with age, time periods and season. The highest risk of malaria infection was among children under the age of five. There was a strong seasonal variation of malaria incidence.

To explore predictors of malaria transmission in Botswana, a generalized geo-statistical spatial model was applied to select significant variables from 50 putative explanatory variables belonging to eight environmental data themes. By using this model, a predicted smooth risk map was produced at unobserved areas for this country (Craig *et al.* 2007).

Space-time distribution of the malaria mosquito *An. arabiensis* was examined to explore environmental factors for vector control in Sudan (Ageep *et al.* 2009). GIS/RS and global position system (GPS) tools were used to assist the association between breeding site characteristics and increased risk of larvae population.

Clements *et al.* (2009) applied Bayesian Poisson regression models to examine the spatio-temporal variation of malaria incidence in Yunnan, China. They found strong associations of malaria incidence with both rainfall and maximum temperature. This study did not include other factors like socio-economic factors but they found that the spatial random effects map was in accordance with the poverty map of Yunnan. However, they indicated that the underlying causes of identified clusters of malaria transmission in south-west and northern Yunnan remain to be determined.

Recently, time series analysis has been used to examine the relationship between malaria transmission and risk factors. For example, Himendan *et al.* (2007) investigated the role of climatic variables and irrigated agriculture in the seasonality of malaria transmission in eastern Sudan using a time-series analysis. In Brundi, Gomez-Elipe *et al.* (2009) found that NDVI, mean maximum temperature, rainfall were predictors of monthly malaria cases in the Karuzi highlands in terms of autoregressive integrated moving average (ARIMA) model. Tian *et al.* (2008) applied ARIMA models to assess the relationship between climatic factors and malaria incidence in Yunnan, China. Lin *et al.* (2009) conducted time series analysis to evaluate the relationship between *falciparum* malaria in the endemic provinces and the imported *falciparum malaria* in the non-endemic provinces in China. Hu and colleagues (1998) conducted regression analyses and found that climate variables (e.g. annual temperature and rainfall), forest coverage, elevation and distance closer to the international border were associated with high malaria incidence during 1986-1996 in Yunnan. In a temperate city Jinan, north China, a clear association between temperature and malaria cases was found. SARIMA models indicated a 1°C increase in maximum temperature may cause approximately 7.7%−12.7% rise in malaria cases, while a 1°C rise in minimum temperature may cause a 11.8%−15.8% increase (Zhang *et al.* 2010).

To examine the exposure–response relationship and the distributed lag effects on malaria, a distributed lag nonlinear model (DLNM) was used to estimate the effects of temperature, rainfall and relative humidity on malaria transmission. Kim and colleagues (2012) reported that while taking the lag time into account, malaria transmission in temperate areas is highly dependent on climate factors. Additionally, lagged estimates of the effect of rainfall on malaria are consistent with the time necessary for mosquito development and *P.vivax* incubation in the temperate regions.

2.5 Previous studies in Yunnan Province, China

Although malaria is a significant public health problem in Yunnan Province, China, there were only four studies which have explored the distribution of malaria incidence and risk factors of malaria transmission in this endemic region (Hu *et al*. 1998; Tian *et al*. 2008; Clements *et al*. 2009; Hui *et al.* 2009). All these studies focused on the spatio-temporal distribution of malaria incidence but the pattern of malaria deaths remains unknown in Yunnan. However, the number of malaria deaths in Yunnan, which was greater than any other province in China, greatly contributed to the burden of disease in Yunnan. All malaria deaths in China in 1995 and 1998 were reported from Yunnan. To understand the spatial pattern of malaria deaths over time would help to identify high risk locations and better support malaria control interventions and resource allocation in this endemic region.

Previous four studies examined the relationship between climatic factors and malaria incidence at a county level in the whole Yunnan Province (Hu *et al*. 1998; Tian *et al*. 2008; Clements *et al*. 2009; Hui *et al.* 2009). One study took into account of economic (e.g. income) and environmental (e.g. rainfall, temperature, forest coverage, elevation and distance to the border) factors, but this study only used annual data (Hu *et al*. 1998). The other three studies used monthly weather and malaria data (Tian *et al*. 2008; Clements *et al*. 2009; Hui *et al.* 2009). The use of annual and monthly average values of climatic variables such as temperature and rainfall could mask the dynamic relationship between climatic factors and malaria because short term variations (e.g. weekly/daily) in temperature/rainfall may be more important than their annual/monthly differences.

Finer temporal scales (e.g. daily and weekly) of malaria cases and climatic variables would provide a more detailed local assessment of malaria risks and their determinants, particularly in the identified high risk areas of Yunnan. Furthermore, daily and weekly data could provide a good lead time for developing a preliminary malaria early warning system in Yunnan.

In a recent study, we used the malaria incidence as the outcome measure rather than SPR since the daily surveillance data of notifiable diseases (including malaria) are available nationwide in China while SPR data are only available for some areas. The estimate of malaria severity using the malaria incidence is convenient and accessible for public health professionals in different regions. The majority of previous studies used a key surveillance indicator – the malaria incidence to estimate the severity of malaria transmission. However, to accurately estimate the malaria incidence is challenging in China. The local population sizes might be under- or overestimated because census is only carried out once every 10 years in China. Thus, the malaria incidence might be inaccurate due to limited health care resources or under- or overestimate of population sizes. It is important to estimate the burden of malaria accurately for planning public health interventions. The laboratory confirmed malaria cases were unevenly distributed over space and time in China. Slide positivity rate (SPR) is an important monitoring indicator in the malaria annual reporting system. SPR is defined as the number of laboratory-confirmed positive slides examined per 100 slides from fever patients, which has been monitored since the 1980s in China. While, SPR is monitored only in malaria endemic regions and reported through the malaria annual reporting system, which is different from the daily surveillance system. These two surveillance systems are not completely matched. Changes in SPR might provide a useful estimate of changes in the incidence of malaria. For example, SPR has been used as an important measure to estimate the incidence of malaria in Uganda (Jensen *et al*. 2009). It has also been used to evaluate the effectiveness of a malaria control program on the island of Principe (Lee *et al*. 2010). Some studies have demonstrated that SPR has steadily decreased with the decline in the malaria incidence (Lee *et al*. 2010), while others found that the annual parasite index (API) increased, but SPR kept steady at the same level over 20 years (Metzger *et al*. 2009). Therefore, it is important and necessary to examine the role of SPR in malaria transmission in China, particularly in Yunnan. To evaluate malaria incidence using microscopic surveillance indicator would provide more accurate estimate of malaria transmission in Yunnan.

2.6 Summary

GIS and spatio-temporal techniques have been applied to support the development of malaria identification, monitoring and surveillance-response strategies. Socio-ecological changes were associated with the distribution and intensity of malaria transmission. Furthermore, other factors like international travel and cross-border movement increase the potential for re-emergence of malaria in some regions. Uncontrolled land clearance and urbanization were related to changes of mosquito habitats. Some studies considered only one set of variables such as climate variability, and do not account for socio-ecological factors or surveillance indicators such as socio-demographic changes or interactions between climate variables and socio-economic factors. Relatively little research has been conducted to examine the association between socio-ecological variability/changes and malaria transmission in China. Therefore, there is a clear need to further assess the epidemic patterns of malaria, identify high risk areas of this disease and to explore major risk factors of its transmission in malaria endemic region – Yunnan, China. The findings of this research may be applied to other countries with similar malaria endemic in the world.

2.7 Research gaps

According to the literature, current research gaps include that:

1. Spatial and temporal patterns and seasonal variability of malaria deaths remain unclear and should be assessed in Yunnan Province. The high risk locations and periods of malaria mortality need to be examined.

2. The quantitative relationship between socio-ecological variables and the transmission of malaria in the identified high risk areas needs to be examined in more details using a finer temporal scale (e.g. daily/weekly) because previous studies have only examined this issue using annually/monthly data, which could mask the dynamic relationship between socio-ecological factors and malaria.

3. It is important to evaluate whether the microscopic surveillance indicator (e.g. slide positivity rate) can be used to predict the transmission of malaria in China, particularly in Yunnan Province, after taking into account other socio-ecological variables in the modelling process.

These knowledge gaps provide the rational for three empirical studies (chapters 4-6) in the PhD thesis.

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Chapter 3: **Research Design and Methods**

This chapter describes the general research design and methods, given that the detailed and specific materials and methodologies are presented in each results chapter. Chapter 4 (i.e. manuscript I) describes the spatial and temporal patterns of malaria in Yunnan Province, China; Chapter 5 (i.e. manuscript П) identifies high risk areas for malaria in Yunnan Province and examines the effects of climatic variables on the transmission of malaria in the identified high risk areas; Chapter 6 (i.e. manuscript Ш) integrates socio-ecologic factors with malaria incidence and demonstrates the usefulness of the slide positivity rate in estimating the malaria incidence.

3.1 Study area

This research specifically focuses on the patterns and determinants of malaria transmission in Yunnan Province, China. Yunnan is located in south China at 21°08′-29°16′ north latitude and 97°31′-106°12′ east longitude, with Myanmar in the west and Laos and Vietnam in the south with a 4,060 kilometre border. Yunnan Province, includes 16 prefectures and 128 counties, and in 2010 had a population of 45.9 million. There are seven climatic zones in Yunnan including: the north tropic zone, the south sub-tropic zone, the middle sub-tropic zone, the north sub-tropic zone, the south temperate zone, the middle temperate zone and highland climate zone. The seasonal mean temperature varies from 10 °C to 15 °C and daily mean temperatures range from 12 °C to 20 °C. It has approximately 1,100 mm annual rainfall, nearly 85% of which occurs between May and October. The elevation varies from less than

100 meters to over 6,000 meters. The complex and favourable geographical, ecological and climatic conditions provide multiple mosquitoes habitats.

3.2 Study design

The potential impact of socio-ecological variation on the transmission of malaria for the period of 1990–2010 in Yunnan Province was assessed in three population-based epidemiological studies. In the first study (chapter 4), spatial distribution, seasonal patterns and geographic variations of malaria, were examined at a county level using SaTScan and geographic information system (GIS) techniques. Some high risk cluster areas were clearly identified. In the second study (chapter 5), the effects of climatic variables on malaria infection in the primary cluster area were estimated using a distributed lag nonlinear model (DLNM). In the third study (chapter 6), the association of the incidence of malaria infection with socio-ecological variables was assessed using multiple linear regression models to assess the risk factors for the transmission of malaria in Mengla County, which is located in the secondary cluster area. There are several reasons to choose Mengla as a study site: 1) It is a high malaria endemic area in China. Its annual malaria incidence (400.4/100,000) was ranked top six among the 2,353 counties of China during 1994–1998 (Gao *et al.* 2003). 2) Mengla was identified as one of the 75 first line counties in China for Malaria Elimination Program (2010–2020). 3) Mengla has a 740 km border line. The increased travel across international border (China-Myanmar and China-Laos) aggravates the burden of malaria.

3.3 Data collection and management

3.3.1 Data collection

3.3.1.1 Malaria data

Malaria is a notifiable infectious disease in China. A computerized reporting system for notifiable infectious diseases has been established, which links data from all of China's provinces via China Centre for Disease Control and Prevention (China CDC) at each provincial, prefecture, county and township administrative level. Malaria data include malaria cases and deaths which are required to be reported to China CDC through the National Notifiable Diseases Surveillance System (NNDSS). These cases and deaths were identified according to the unified diagnostic criteria issued by Chinese Ministry of Health, which includes the definitions of clinically diagnosed and laboratory confirmed cases (Ministry of Health of the People's Republic of China, 2006). Malaria cases were identified by microscopy and/or rapid diagnosis test and/or clinic symptoms. A patient who is diagnosed with malaria case and died from this disease is recorded as a malaria death. The malaria deaths were classified according to the International Classification of Diseases, ninth version (ICD-9) (ICD-9: 084). A computerised dataset was obtained from Yunnan Provincial CDC, including monthly data from 1991 to 2010, and daily data from 1 January, 2005 to 31 December, 2010, with patients' information, e.g. age, gender, the onset date of disease and residential address. Annual malaria incidence was calculated by using the number of malaria cases as a numerator and the local population as a denominator. Slide positivity rates is defined as the number of laboratory-confirmed positive slides examined per 100 slides, expressed as a percentage. Blood smear of febrile patients were examined and confirmed by microscope and/or by rapid diagnostic test. The calculation of SPR is the number of positive slides divided by total slides examined and multiplied by 100.

3.3.1.2 Climate data

Climate data were obtained from the Chinese Meteorological Administration (http://www.cma.gov.cn) including all 36 meteorological stations across Yunnan Province. The data included daily minimum, mean and maximum temperatures (°C), rainfall (mm), and relative humidity (%) for the period of 1 January, 2005 to 31 December, 2010. The annual average relative humidity, mean maximum temperature, mean minimum temperature and rainfall for Mengla were provided by the Mengla County Bureau of Meteorology for the study period.

3.3.1.3 Demographic and economic data

Demographic data of each county for the study period were obtained from the Yunnan Bureau of Statistics. The information on annual farmer income, i.e. average income per capita of farmers, was retrieved from the Mengla Bureau of Statistics.

3.3.2 Data management and geocoding

Information from the electronic records was extracted and coded for health outcome, climatic variables and other socio-demographic factors. Both malaria incidence and mortality were calculated and used as response variables. Weekly/annual average climatic variables such as average minimum/maximum temperature, relative humidity, rainfall and socio-economic factors as well as microscopy indicator like slide positivity rate of fever patients, etc. were calculated and used as independent variables. Data on disease and population were geocoded and matched with the boundary map for each county. Each county contained the latitude and longitude of its capital location. Various spatial data layers including malaria cases and incidence, malaria deaths and mortality were created using GIS.

3.4 Data linkages

Yunnan Province consists of 128 counties. Malaria cases and deaths with residential address were coded using the county's name and county code, and linked to the corresponding polygon on a digital boundary map of Yunnan Province using ArcGIS and Microsoft Excel softwares.

3.5 Statistical analysis

The statistical analysis was conducted at a county level according to the following flowchart and there were three parts in the empirical analysis of the spatial-temporal relationships between socio-ecological variability and the transmission of malaria: (1) visualisation of data, (2) exploratory data analysis, and (3) model building.

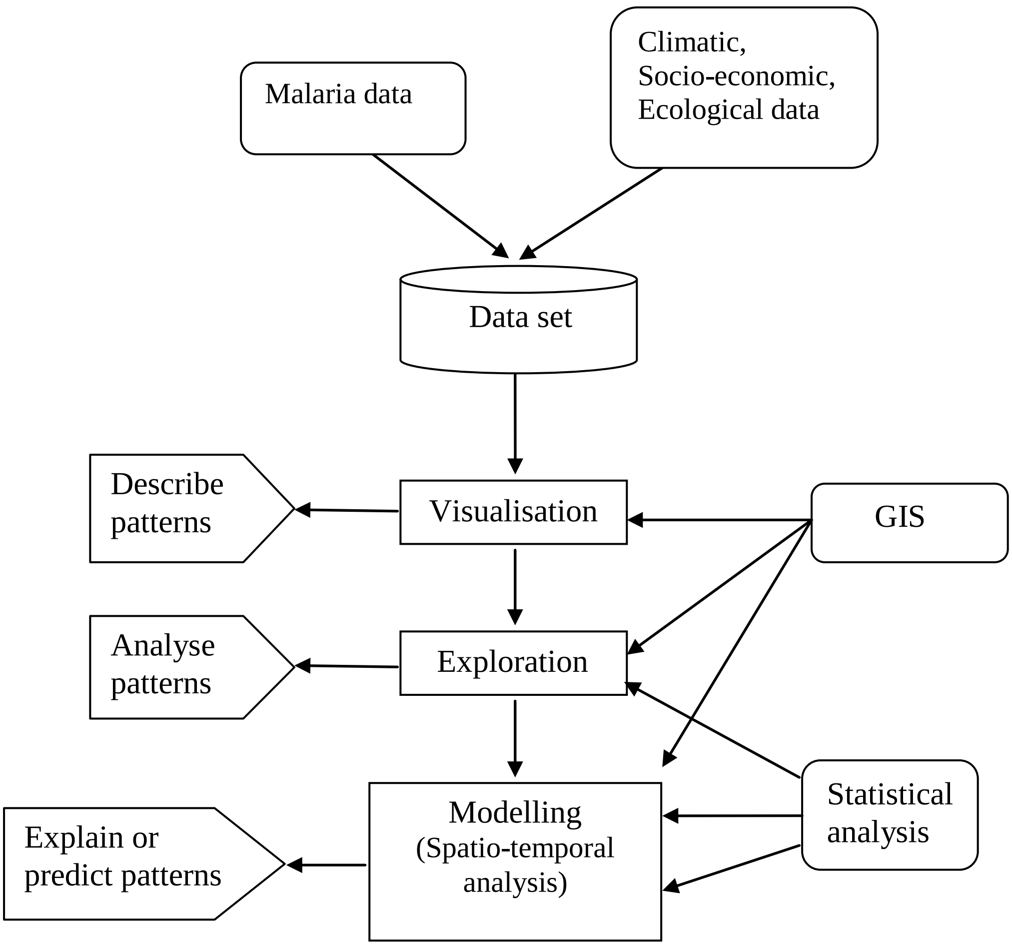

Figure 3.1 Conceptual framework of spatial epidemiological data analysis (Minor modification based on Pfeiffer *et al.* 2008)

3.5.1 Visualisation of data

The location for each case and death of malaria was geo-coded with the digital boundary map at a county level. ArcGIS was used to create choropleth maps to show outputs of spatial and temporal analysis. The annual/seasonal malaria infection and relative risk were mapped to display the dynamic changes of spatial-temporal patterns of malaria transmission. The visualisation of these maps will facilitate accurate identification of high risk areas and peak season for further assessment of potential risk factors in Yunnan Province.

3.5.2 Exploratory analyses

3.5.2.1 Univariate analysis

Univariate analyses were performed to examine the characteristics of each variable in the dataset, including dependent variables (i.e. malaria cases/deaths and malaria incidence/mortality) and independent variables (i.e. temperature, rainfall, relative humidity, income and slide positivity rate (SPR)). Inter-correlation of independent variables was assessed (i.e. histogram and scatter plot). To avoid skewed distribution of malaria incidence, the square root transformation was applied to assure the normality of its distribution for temporal analysis (chapter 6). Missing values (≤4%) were checked during the process of data analyses and the cases/deaths with any missing values were excluded from the analyses.

3.5.2.2 Bivariate analysis

Spearman correlation analyses were conducted to assess the relationship between malaria and risk factors including climatic, socio–economic and ecological variables. In this research, the issue of multicollinearity was carefully considered. For example, some variables were highly correlated (e.g. minimum temperature and mean temperature: $r = 0.91$). Therefore, these highly correlated variables were separately analysed in different models.

3.5.2.3 Spatio-temporal cluster analysis

Spatial and temporal cluster analyses were applied to detect spatial clusters or high risk locations of malaria using SaTScan technique. The malaria mortality/incidence at a county level in Yunnan Province were plotted by year and by season (for malaria mortality) to observe the annual and seasonal fluctuation. Spatial and seasonal cluster analyses were performed using the discrete Poisson model to test the null hypothesis that malaria counts are randomly distributed over space and/or in different seasons at a county level.

Spatial scan statistics were conducted to detect spatial clusters of malaria deaths/cases using SaTScan9.1 software. The SaTScan software set circular windows of various sizes, and moved each window over the time. Whenever the window encountered a new case, a likelihood function was calculated to test for elevated risk within the window in comparison with those outside the window. The likelihood function for a specific window was proportional to (Kulldorff 1997):

$$\left(\frac{c}{E[c]}\right)^{c}\left(\frac{C-c}{C-E[c]}\right)^{C-c} I()$$

where C is the total number of cases/deaths, c is the observed number of cases/deaths within the window, E[c] is the expected number of cases/deaths within the window, and C – E[c] is the expected number of cases/deaths outside the window. The indicator function I () is 1 when cases/deaths in the window are more than expected, otherwise it would be 0. A relative risk (RR) is the estimated risk within the cluster divided by the estimated risk outside the cluster (Kulldorff 2010).

3.5.3 Multivariable modelling

3.5.3.1 Multiple linear regression analysis and logistic regression model

To examine the impact of socio-ecological factors on malaria transmission, multiple linear regression models were used to examine if the slide positivity rate (SPR) can predict the malaria incidence after adjustment for confounding variables. To identify the spatial changes of malaria mortality, logistic regression models were performed to define whether an increase/decrease of malaria deaths occurred in each county for the different periods of time.

3.5.3.2 Distributed lag non-linear modelling

Distributed lag non-linear model (DLNM) with Poisson link was used to examine the effects of climatic variables on the transmission of malaria after adjustment for seasonality and over-dispersion. A DLNM model was applied to explore the non-linear effects and lag structures of temperature, relative humidity and rainfall on both types of malaria parasites (*P.vivax* or *P.falciparum* malaria) using "dlnm" functions of R package.

Software packages used in this study include Microsoft Excel (2007), SPSS (PASW Statistics, Version 18), SaTScan (Version 9.1, Martin Kulldorff, Boston, MA, USA), ArcGIS 9.3 (ESRI Inc., Redlands, CA, USA), SAS 9.2 (SAS Institute Inc., Cary, NC, USA), and R (The R Foundation for Statistical Computing, version 2.15.2, 2012 http://cran.ms.unimelb. edu.au/).

3.6 Ethics

An ethical approval was granted by the Human Research Ethics Committee, Queensland University of Technology (#1000000573).

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Chapter 4: **Spatial patterns of malaria reported deaths in Yunnan Province, China**

Citation

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YB was the principal author of the manuscript, designed the research, carried out data collection, performed data analysis, and wrote the manuscript. WH and ST contributed to the conceptual development and manuscript writing. HY and XZ assisted with interpretation of results. WY and YG provided feedback on writing of the manuscript. All authors contributed to the manuscript edit, review and revising, and approved the final version of the manuscript.

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Chapter 5: **Impact of climate variability on *Plasmodium vivax* and *Plasmodium falciparum* malaria in the high risk area of Yunnan Province, China**

Citation

Bi Y., Yu W., Hu W., Lin H., Guo Y., Zhou X., and Tong S. Impact of climate variability on *Plasmodium vivax* and *Plasmodium falciparum* malaria in the high risk area of Yunnan Province, China

Date submitted

Invited to revise

Contribution of authors

YB designed the research protocol and wrote the manuscript. YB and HL performed field data collection. WY, YB and YG conducted data management and analysis. ST, WY and WH contributed to interpret the results and assisted in writing the manuscript. XZ contributed to the manuscript by providing intellectual feedback on draft.

Abstract

Background

Malaria remains a public health problem in the remote and poor area of Yunnan Province, China. Yunnan faces an increasing risk of imported malaria infections from Mekong-River neighboring countries.

Aims

This study aimed to identify the high risk area of malaria transmission in Yunnan Province, and to estimate the effects of climatic variability on the transmission of *Plasmodium vivax* and *Plasmodium falciparum* in the identified area.

Methods

We identified spatial clusters of malaria cases using spatial cluster analysis at a county level in Yunnan Province, during 2005-2010, and estimated the weekly effects of climatic factors on *P.vivax* and *P.falciparum* based on a dataset of daily malaria cases and climatic variables. A distributed lag nonlinear model (DLNM) was used to estimate the impact of temperature, relative humidity and rainfall on both types of malaria parasite after adjusting for seasonal and long-term effects.

Results

The primary cluster area was identified along the China–Myanmar border in western Yunnan. A 1 °C increase in minimum temperature was associated with a lag 4 to 9 weeks relative risk (RR), with the highest effect at lag 7 weeks for *P.vivax* (RR=1.03 (95% CI, 1.01, 1.05)) and 6 weeks for *P.falciparum* (RR=1.07 (95% CI, 1.04, 1.11)); a 10-mm increment in rainfall was associated with RRs of lags 2-4 weeks and 9-10 weeks, with the highest effect at 3 weeks for both *P.vivax* (RR=1.03 (95% CI, 1.01, 1.04)) and *P.falciparum* (RR=1.04 (95% CI, 1.01, 1.06)); and the RRs with a 10%

rise in relative humidity were significant from lag 3 to 8 weeks with the highest RR of 1.24 (95% CI: 1.10, 1.41) for *P.vivax* at 5-week lag.

Conclusion

Our findings suggest that the China-Myanmar border is a high risk area for malaria transmission. Climatic factors are among major determinants for malaria transmission in this area. The estimated lag effects for the association between temperature and malaria are consistent with the life cycle of malaria parasite in mosquito vector. These findings will be useful for malaria surveillance-response systems in the Mekong-River region.

Key Words

Plasmodium vivax, *Plasmodium falciparum*, spatial cluster area, distributed lag nonlinear model, Climatic variables, China-Myanmar border area

5.1 Introduction

Malaria, a wide-spread mosquito-borne disease, affects 106 countries around the world.(World Health Organization: Global Malaria Programme 2011) It is one of the leading causes of morbidity and mortality in many developing countries, responsible for about 216 million cases and approximately 665,000 deaths worldwide in 2011.(World Health Organization: Global Malaria Programme 2011) In China, malaria remains a major public health issue, with 205,864 confirmed and 395,837 suspected cases and 158 reported deaths from 2005 to 2010, despite national malaria control efforts and international support in the past decades.(Lin *et al.* 2009; Clements *et al.* 2009; Zhou *et al.* 2006, 2007; Zhou *et al.* 2008, 2009; Zhou *et al.* 2011a; Zhou *et al.* 2011b) The endemic situation is even worse in the remote and poor border area of southern China.(Sarah *et al.* 2008; Zhu *et al.* 1994) For example, in Yunnan Province, malaria incidence was 49.5/100,000 in 2005, with 15,072 confirmed and 26,084 suspected malaria cases and 38 reported deaths.(Zhou *et al.* 2006) More than 11,000 people suffered from malaria each year from 2002 to 2006 with the province having the highest number of malaria cases and deaths in China for more than a decade since the 1990s.(Zhou *et al.* 2006) There are frequent malaria outbreaks in Yunnan, which has devastating effects on mental, physical, social and economic development of individuals and villages affected.(Zhu *et al.* 1994; Xu *et al.* 1997)

A variety of factors are known to affect the transmission of malaria.(Koram *et al.* 1995; Lindsay *et al.* 1998; Craig *et al.* 2004a; Craig *et al.* 2004b; Al-Taiar *et al.* 2009) In particular, climatic factors are considered to play an important role in the spatial and temporal distribution of malaria.(Craig *et al.* 1999; Tanser *et al.* 2003)

The relationship between climatic variables and malaria transmission has been reported in many countries, mostly in Africa,(Craig *et al.* 2004a; Hay *et al.* 2002; Githeko *et al.* 2001; Paaijmans *et al.* 2009) Asia,(Lin *et al.* 2009; Clements *et al.* 2009; Kim *et al.* 2012) South America and Latin America.(Gagnon *et al.* 2002; Prothero 1995) Malaria has been identified as one of the most climate sensitive diseases, (Githeko *et al.* 2000) with studies suggesting significant associations between temperature and malaria incidence. (Clements *et al.* 2009; Kim *et al.* 2012; Kleinschmidt *et al.* 2001) Relative humidity (Bouma *et al.* 1996; Zucker 1996) and rainfall have also been associated with malaria transmission.

However, few studies have been conducted to examine the impact of climatic variables on malaria transmission in high risk area along the border area of Yunnan Province,(Bouma *et al.* 1996; Zhou *et al.* 2005; Nkurunziza *et al.* 2010) particularly in the Mekong river region. The Mekong neighboring countries share similar climatic and environmental conditions, and suffer from increasing risk of imported malaria by inter-country population movements. The Asian tropic zone is well known as a malaria endemic region,(Wiwanitkit 2008) and Yunnan Province is located in this zone, which shares a 4060 kilometer border with Myanmar, Laos and Vietnam (Figure 1-A). In 2005, the number of malaria cases in Yunnan accounted for more than one third (15,072/42,319) of the total cases in China.(Zhou *et al.* 2006) Yunnan faces a serious problem of malaria becoming endemic, particularly due to imported malaria along its border area.(Zhou *et al.* 2006) 67% of *Plasmodium falciparum* cases (454/678) were imported from neighbouring countries in Yunnan in 2008, where mobile population are vulnerable to malaria infection.(Sarah *et al.* 2008)

It is important to identify high risk area on malaria transmission at the regional level, and further to focus on at the micro level to assist determining risk factors and developing the optimal strategies for local malaria control and prevention. The spatial scan statistic method has been widely applied to identify cluster regions and periods in malaria transmission.(Zhang *et al.* 2008; Hui *et al.* 2009; Coleman *et al.* 2009; Bi *et al.* 2012) The distributed lag nonlinear model (DLNM) is a flexible model to show different delayed effects of the non-linear exposure–response relationship,(Gasparrini *et al.* 2010) and is increasingly used to examine the effects of temperature, rainfall and relative humidity on malaria transmission.(Kim *et al.* 2012; Jusot *et al.* 2011) This study aimed to identify a high risk area of malaria at a county level in Yunnan Province, and to examine the effects of climatic variability on the transmission of *Plasmodium vivax* (*P.vivax*) and *Plasmodium falciparum (P.falciparum)* in the high risk area of Yunnan Province, China.

5.2 Methods

5.2.1 Study area

Yunnan Province has an area of 394,000 square kilometers and a population of 45.9 million according to the 2010 census. The province includes 16 prefectures, 128 counties and over 1,500 townships. The annual rainfall is about 1,100 mm, the seasonal mean temperature varies from 10 °C to 15 °C, and daily mean temperatures range from 12 °C to 20 °C. A bimodal epidemic pattern has been reported in Yunnan Province with the first peak in May–July and the second peak in October–November.(Hui *et al.* 2009) *P. vivax* and *P. falciparum* have been observed to be co-existing in the province, with *P. vivax* being the dominant species. The principal vectors of malaria are *Anopheles* (*An.*) *minimus* and *An. sinensis* in this region.(Zhu *et al.* 1994)

5.2.2 Malaria cases and demographic data

In China, malaria is a notifiable infectious disease through the National Notifiable Diseases Surveillance System (NNDSS). Daily malaria cases and deaths are reported to the China Center for Disease Control and Prevention (China CDC) based on township, county, prefectural, provincial and national levels since 2005. These cases and deaths were identified according to the unified diagnostic criteria issued by Chinese Ministry of Health.(Ministry of Health of the People's Republic of China 2006) Our investigations targeted Yunnan Province, which contains malaria high-risk border areas of southern China. We obtained information on daily malaria cases at a county level from the Yunnan Center for Disease Control and Prevention for the period from 1 January, 2005 to 31 December, 2010, including information about the date of onset, place of residence, type of parasite/s, diagnostic methods used (microscope and/or rapid diagnostic test). Weekly *P.vivax* and *P.falciparum* malaria counts were calculated from daily records. A total of 44,877 malaria cases were reported during the study period. Eight records with missing date of birth and seven records with the reported dates in December 2004 were excluded. We excluded a further 948 cases (948/44884=2.1%) as their residence was not in Yunnan Province during the study period. A total of 41,578 malaria cases (including 31,704 *P.vivax* and 9,874 *P.falciparum*) were included in the analysis. Demographic data of each county were obtained from the annual book of the Yunnan Bureau of Statistics.

5.2.3 Climate data

Temperature, relative humidity and rainfall data from 1 January, 2005 to 31 December, 2010 were obtained from the Chinese Meteorological Administration (http://www.cma.gov.cn). There are 36 weather stations in Yunnan Province, and daily climate data are available in each station. In this study, two weather stations (Tengchong and Baoshan) were located at the identified high risk area of malaria transmission. The daily averaged climate data in these two stations were used to explore the relationship between climate variations and malaria. Weekly average values of minimum, maximum and mean temperatures, relative humidity and the weekly total rainfall were calculated from the daily data.

5.2.4 Data analysis

Spearman's correlation between weekly climatic variables (temperatures, relative humidity and rainfall) and malaria cases (*P.vivax* and *P.falciparum*) was examined using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) to analyse bivariate relationships between two types of malaria parasite and potential climatic factors.

Spatial cluster analysis was conducted using Spatial Scan Statistics (SaTScan software, version 9.1, Martin Kulldorff, Boston, MA). A discrete Poisson model was used to identify purely spatial clusters of malaria incidence, for each county of Yunnan Province by year between 2005 and 2010. The cluster analysis was used to identify high risk areas in this study.

A Poisson regression model combined with distributed lag non-linear model (DLNM) was used to examine the effects of temperature, relative humidity and rainfall on the number of malaria cases as follows. The lag effects of climatic variables on numbers of *P.vivax* or *P.falciparum* malaria were separately examined.

First, the temperature indicator was selected by a comparison of Akaike's Information Criterion (AIC) values for the corresponding models of mean, minimum and maximum temperatures. Minimum temperature was found to be a better predictor and was thus used as the temperature indicator.

Second, the cross-basis framework was built with natural cubic splines for temperature (degrees of freedom (*df*=5)) and its lag (*df*=5) along with relative humidity (*df*=4) and its lag (*df*=4). A polynomial function was used for rainfall (*df*=4) and its lag (*df*=4). The maximum lag was selected up to 10 weeks for all variables according to previous work (Kim *et al.* 2012).

Third, the Poisson regression model was applied:

$$Ln(E(Y_t)) = \alpha + \sum_{i=1}^{p} (\beta_i x_i) + \mu_j season_j + s(w_j, 7)$$

Where t refers to the week of the observation; (Y_t) denotes the observed weekly malaria counts on week t; x_i denotes the cross-basis of temperature and relative humidity when their effects on malaria were examined, and rainfall and temperature when the effects of rainfall on malaria were examined; season$_j$ denotes seasonal effects that were controlled by a categorical variable consisted of dry (November–April) or wet (May–October) season; w_j is the week of the year j (e.g. 1, 2,…,52*)* and natural cubic splines with 7 degrees of freedom were used to adjust for seasonal and long-term effects; α is the intercept term; p is the number of variables; β *a*nd μ are coefficients.

Fourth, we plotted the associations of minimum temperature, relative humidity and rainfall with malaria cases for both parasites. The central value for each climatic variable was identified by the visual inspection of the plots.

Fifth, we repeated the second and third steps with central values of minimum temperature (7 °C), relative humidity (73%) and rainfall (60-mm) which identified by step four.

Finally, parasite-specific risk estimates of weekly malaria cases associated with one unit increase in temperature, relative humidity and rainfall above the central value over different lags were evaluated. We acknowledge that the relationships between relative humidity and rainfall and malaria were non-linear, but using one unit increase in relative humidity/rainfall can reflect the relationship between relative humidity/rainfall and malaria above the centre value.

The residuals were checked to evaluate the adequacy of the model. Sensitivity analyses were performed to make sure that the associations between climate variables and malaria did not change substantially when the degrees of freedom for climate variables changed. All data analyses were conducted using “dlnm” functions of R packages to fit the regression model (The R Foundation for Statistical Computing, version 2.15.2, 2012 http://cran.ms.unimelb. edu.au/).

5.3 Results

5.3.1 Exploratory analyses

Table 5.1 shows the summary statistics of weekly *P.vivax* and *P.falciparum* and climatic variables in the identified primary cluster area of western Yunnan. During the study period, the weekly mean malaria cases were 60.8 for *P.vivax* and 25.3 for *P.falciparum*, respectively. In the total 313 weeks of the study period, there were 27,052 malaria cases (including 19,106 *P.vivax* and 7,946 *P.falciparum*) reported in the identified high risk cluster area. The average values of the maximum, mean and minimum temperatures were 25 °C, 18.5 °C and 14.3 °C, respectively. The average weekly relative humidity and rainfall were 73.1% and 27.3 mm, respectively.

Table 5.1 Summary statistics of weekly malaria cases and weather conditions in the primary cluster area of Yunnan Province, China, 2005–2010

Variables	Mean(SD)	Minimum	Percentile			Maximum
			25%	50%	75%	
Temperature (°C)						
Maximum	25.0(3.4)	8.6	22.8	25.8	27.5	31.3
Mean	18.5(4.3)	5.3	14.8	20.1	22.1	24.9
Minimum	14.3(5.5)	2.1	9.0	15.4	19.7	21.6
Relative humidity (%)	73.1(10)	32.6	66.3	75.2	81	91.9
Rainfall (mm)	27.3(32.2)	0	0.31	16.2	43.9	156.3
Plasmodium parasite						
P.v	60.8(50.3)	5	21	41	96	210
P.f	25.3(24.6)	0	8	15	34	132

P.v: Plasmodium vivax, P.f: *Plasmodium falciparum*

Correlations between weekly malaria cases (*P.vivax* and *P.falciparum*) and weather variables were found to vary. Temperature and rainfall were positively correlated with *P.vivax* and *P.falciparum*. While, relative humidity was positively associated with *P.vivax* but not *P.falciparum*. A positive correlation was also found between relative humidity, rainfall and both *P.vivax* and *P.falciparum*. The three temperature indicators were strongly correlated with each other (Table 5.2). We used minimum temperature in the subsequent analyses, because it gives the best model fit.

The residuals were checked to evaluate the adequacy of the model to ensure they were approximately normally distributed and independent over time (Appendix 5.1). A sensitivity analysis was conducted by changing the *df* for temperature (3–7), relative humidity (3–7), rainfall (3–7) and week of the year (6-15). No substantial changes were found. We changed the *df* (6-15) to control for the week of the year, and the results varied slightly.

Table 5.2 Spearman correlation coefficients between weekly malaria cases and weather variables in the high risk area of Yunnan, China, 2005–2010

Variables	Maximum temperature	Mean temperature	Minimum temperature	Relative humidity	Rainfall	*P. v*
Mean temperature	0.87*					
Minimum temperature	0.72*	0.96*				
Relative humidity	0.07*	0.48*	0.67*			
Rain (weekly cumulation)	0.40*	0.70*	0.80*	0.73*		
P. v	0.37*	0.46*	0.45*	0.35*	0.33*	
P. f	0.32*	0.40*	0.39*	0.30*	0.30*	0.89*

* $p < 0.001$

5.3.2 Spatial analysis

Spatial Scan Statistics identified a most likely cluster of malaria incidences including eight counties (Relative Risk (RR) = 36.10, P < 0.01) in western Yunnan and secondary clusters encompassed 18 counties, with significant relative risks between 1.52 and 4.11 from 17 counties in southern Yunnan and one in North eastern Yunnan

(Figure 5.1). Additional time series analysis was conducted in the most likely cluster area with eight clustering counties bordering Myanmar locating in a subtropical region in western Yunnan.

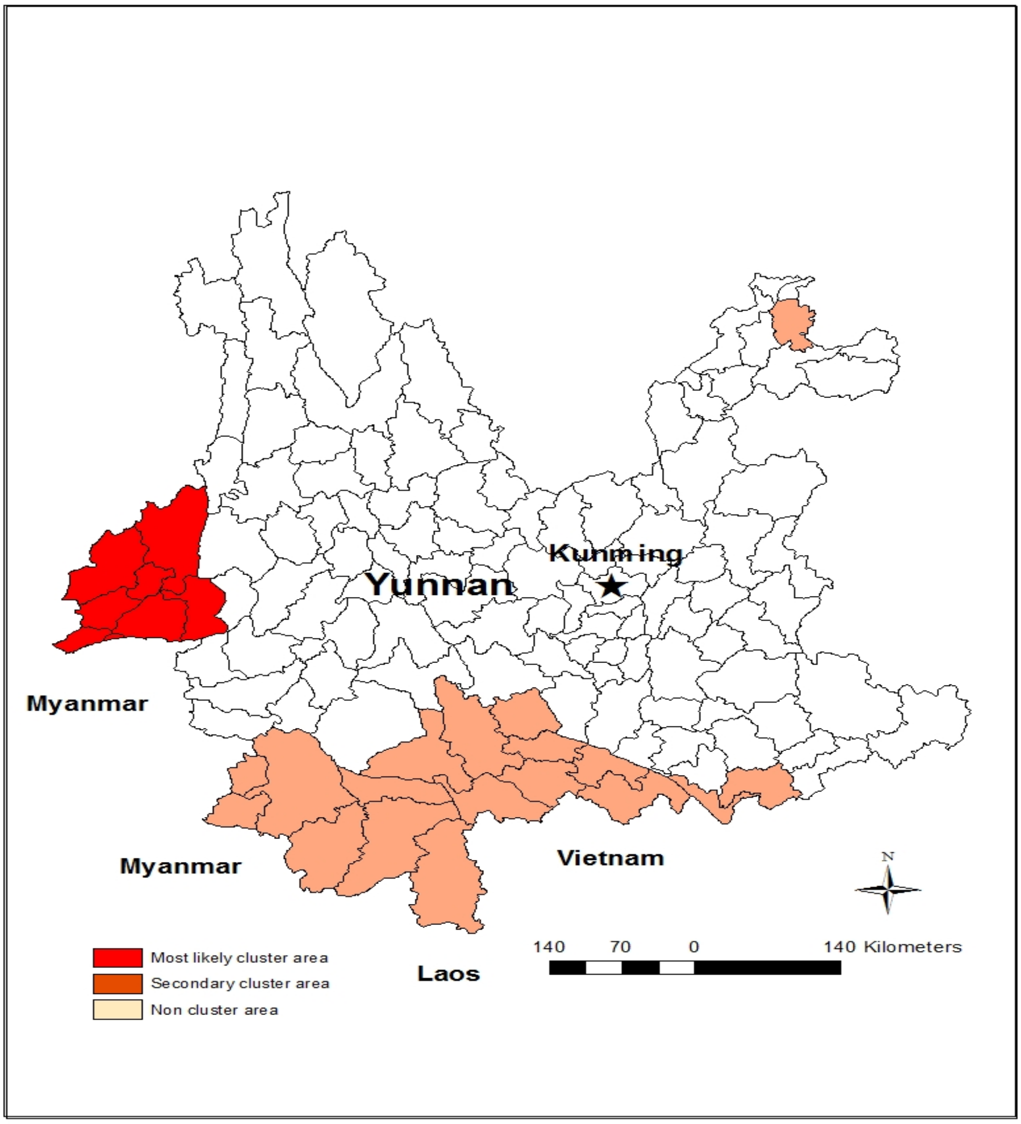


Figure 5.1 Study area: Yunnan Province, China
[using ArcGIS software, version 10.0, USA, Environmental Systems Research Institute]. The primary study area (in red) is the most likely cluster area which is located in the western part of Yunnan Province. Malaria cases in 8 primary cluster counties contributing to 63.9% (28695/44877) of the total cases for Yunnan from 2005 to 2010.

5.3.3 Estimated effects of climate variables on *P.vivax* and *P.falciparum*

Table 5.3 shows estimated single-week and overall lag effects of minimum temperature, relative humidity and rainfall on *P.vivax* and *P.falciparum*. The effects of minimum temperature, relative humidity and rainfall on *P.vivax* (Figure 5.2) and *P.falciparum* (Figure 5.3) were estimated by 1 °C rise in minimum temperature with 7 °C as a reference, by 10% rise in relative humidity with 73% as a reference and by 10-mm rise in rainfall with 60-mm as a reference.

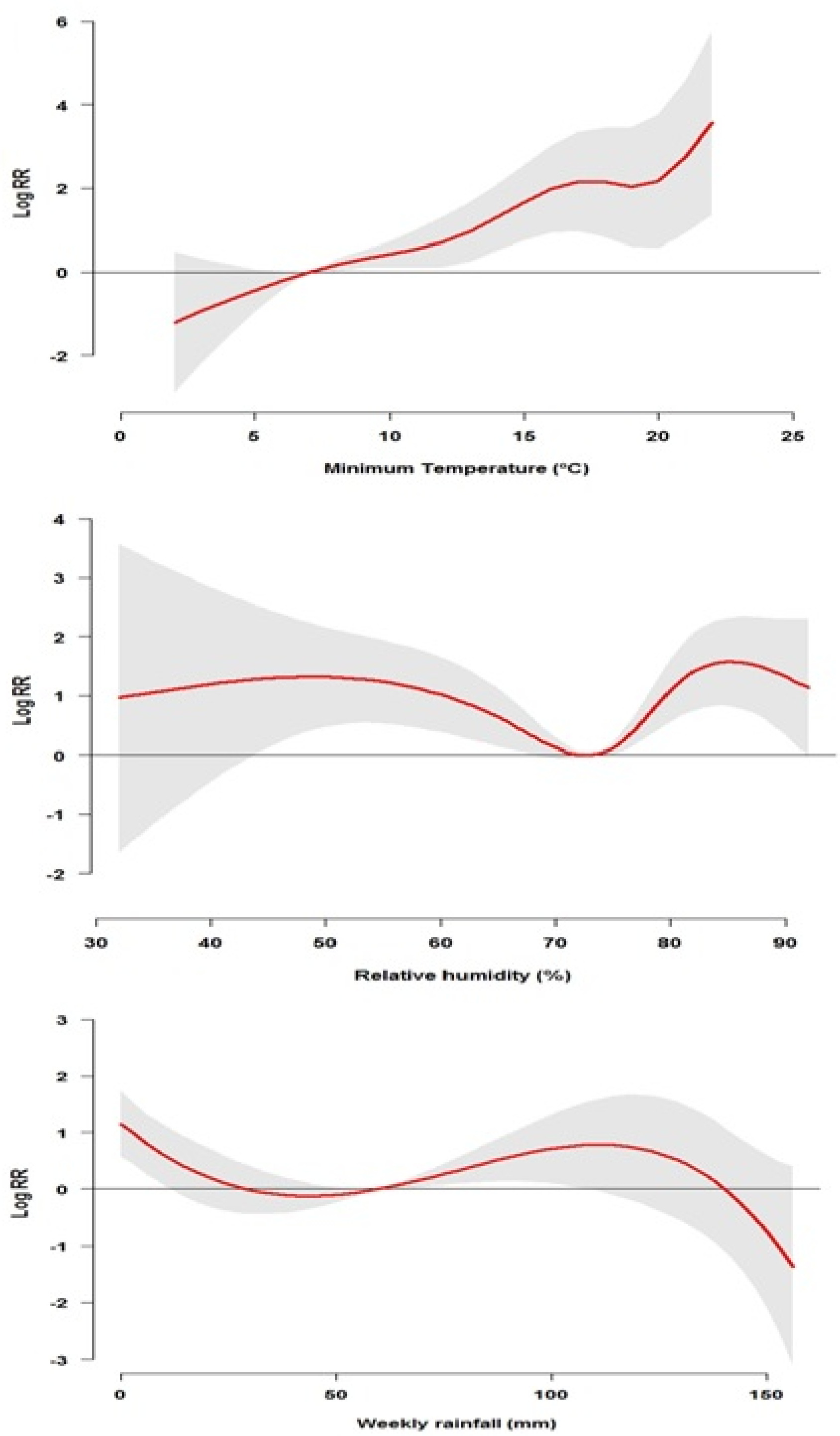


Figure 5.2 The estimated overall effects of minimum temperature, relative humidity and rainfall on *Plasmodium vivax* along the lag of 0–10 weeks in the high risk area of Yunnan, China, 2005–2010

(The red lines are mean relative risks, and grey regions are 95% confidence intervals)

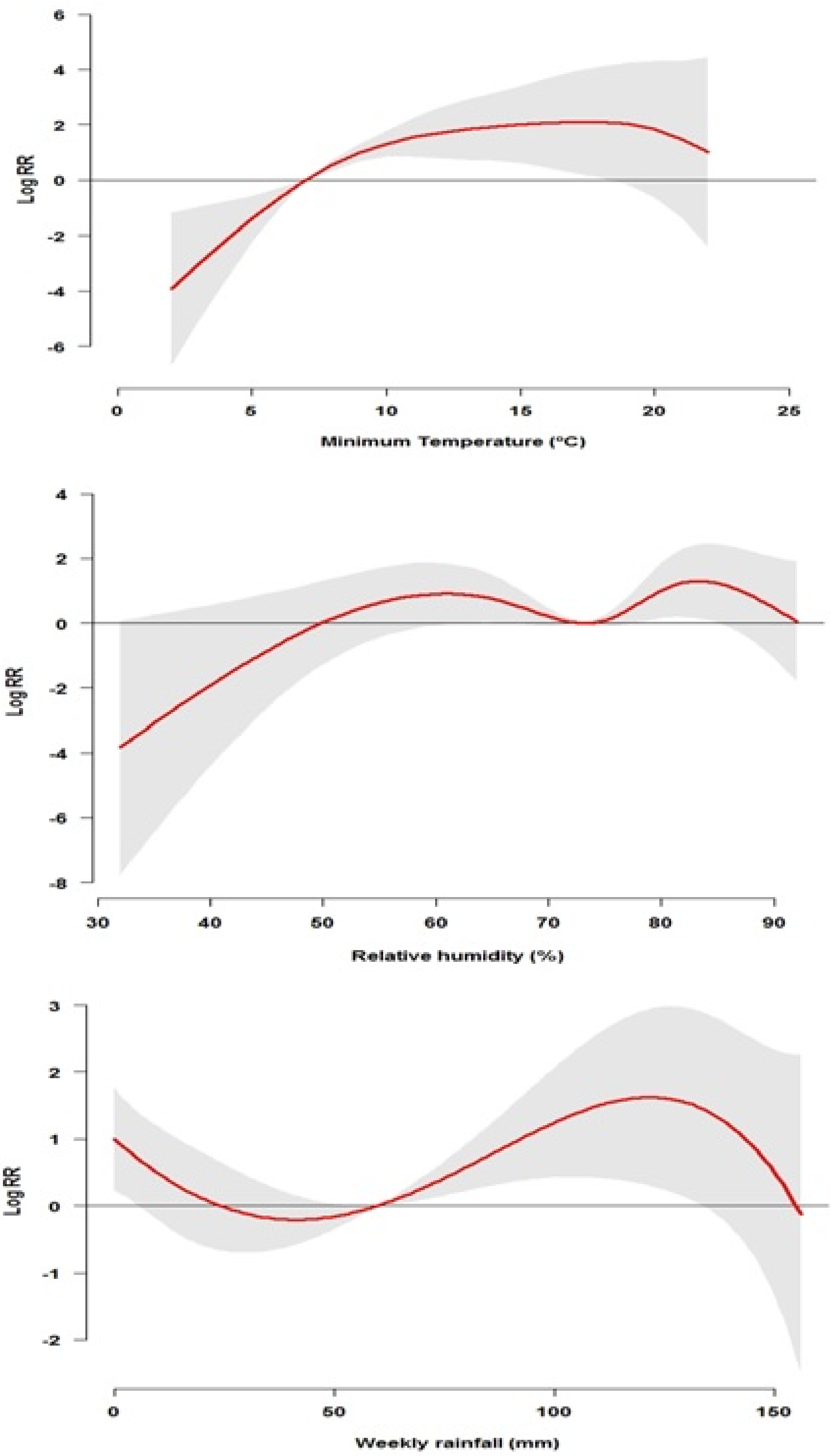


Figure 5.3 The estimated overall effects of minimum temperature, relative humidity and rainfall on *Plasmodium falciparum* along the lag of 0–10 weeks in the high risk area of Yunnan, China, 2005–2010

(The red lines are mean relative risks, and grey regions are 95% confidence intervals)

For *P.vivax,* significant effects of temperature appeared at a lag of 4 weeks. The effects persisted up to 9 weeks. The RR for a 1 °C increase in minimum temperature was associated with 1.02 (95% CI, 1.00, 1.03) at a 4–week lag, and with a maximum RR of 1.03 (95% CI, 1.01, 1.05) at a lag of 5 weeks. Significant effects of relative humidity and rainfall were observed at a lag of 3–8 weeks for relative humidity, and a short lag of 2–4 weeks and a long lag of 9-10 weeks for rainfall, respectively. The RR with a 10% increment in humidity was associated with 1.18 (95% CI, 1.05, 1.33) at a lag of 3 weeks, and a 10-mm increment in rainfall was associated with 1.03 (95% CI, 1.01, 1.05) at a lag of 2 weeks. The overall effects (lag 0–10 weeks) of temperature, relative humidity and rainfall on *P.vivax* cases were significantly observed, with the RRs of 1.19 (95% CI, 1.04, 1.35) for temperature, 4.38 (95% CI, 1.86, 10.30) for relative humidity and 1.18 (95% CI, 1.05, 1.34) for rainfall, respectively (Table 5.3).

For *P.falciparum,* significant effects of temperature were observed at lags of 4–9 weeks and overall 0–10 weeks. Compared to *P.vivax,* the minimum temperature had larger effect on *P.falciparum*. The RR for a 1 °C increase in minimum temperature was associated with 1.06 (95% CI, 1.03, 1.09) at a lag of 4 weeks and 1.74% (95% CI, 1.41, 2.16) at a lag of 0–10 weeks, respectively. *P.falciparum* malaria cases were significantly associated with a 10-mm increase in weekly rainfall at lags of 2–4 weeks and overall 0–10 weeks with similar magnitude as *P.vivax*. A significant association between humidity and *P.falciparum* was not observed at any lags (Table 5.3).

Table 5.3 The weekly lag effects of climate variables on P. vivax and P. falciparum

Lag effects on *P. v*	Minimum temperature (℃)	Relative humidity (%)	Rainfall (mm)
Lag0	1.01 (0.96,1.06)	1.08 (0.85,1.38)	0.99 (0.97, 1.01)
Lag1	0.98 (0.94,1.03)	1.08 (0.93,1.27)	1.02 (0.99, 1.04)
Lag2	0.99 (0.96,1.02)	1.12 (0.95,1.33)	1.03 (1.01,1.05)*
Lag3	1.01 (0.98, 1.04)	1.18 (1.05, 1.33)*	1.03(1.01,1.04)*
Lag4	1.02 (1.00,1.04)*	1.23 (1.10,1.38)*	1.02 (1.00,1.04)*
Lag5	1.03 (1.01,1.05)*	1.24 (1.10,1.41)*	1.02 (0.99, 1.05)
Lag6	1.03 (1.01,1.06)*	1.23 (1.09,1.39)*	1.01 (0.99,1.02)
Lag7	1.03 (1.02, 1.05)*	1.19 (1.07,1.33)*	1.01 (0.99,1.02)
Lag8	1.03 (1.01,1.05)*	1.13 (1.02,1.27)*	1.01 (0.99,1.03)
Lag9	1.02 (1.00, 1.04) *	1.07 (0.93,1.25)	1.02 (1.00,1.04)*
Lag10	1.01 (0.98,1.05)	1.02 (0.83,1.25)	1.02 (1.00,1.05)*
Lag0-10	1.19 (1.04,1.35)*	4.38 (1.86,10.30)*	1.18 (1.05,1.34)*
Lag effects on *P. f*			
Lag0	1.02 (0.95, 1.10)	0.95 (0.55, 1.62)	0.98 (0.96,1.01)
Lag1	1.06 (0.99, 1.14)	0.87 (0.60,1.26)	1.02 (0.99,1.05)
Lag2	1.05 (0.99,1.10)	0.89 (0.60, 1.33)	1.04 (1.01,1.06)*
Lag3	1.05 (0.99, 1.10)	0.98 (0.74,1.30)	1.04 (1.01,1.06)*
Lag4	1.06 (1.03,1.09)*	1.07 (0.82,1.39)	1.03 (1.01,1.06)*
Lag5	1.07 (1.04, 1.11)*	1.11 (0.82,1.51)	1.02 (0.99,1.05)
Lag6	1.07 (1.04,1.11)*	1.12 (0.83,1.51)	1.01 (0.99, 1.04)
Lag7	1.07 (1.03, 1.11)*	1.10 (0.84,1.43)	1.01 (0.98,1.03)
Lag8	1.06 (1.03,1.09)*	1.06 (0.82,1.37)	1.01 (0.98,1.04)
Lag9	1.04 (1.01,1.08)*	1.00 (0.71,1.41)	1.01 (0.99, 1.04)
Lag10	1.02 (0.97, 1.08)	0.94 (0.57, 1.54)	1.03 (0.99, 1.06)
Lag0-10	1.74 (1.41,2.16)*	1.06 (0.16, 6.78)	1.23 (1.03,1.46)*

5.4 Discussion

In this study, we identified a high risk area of malaria transmission in Yunnan Province, southern China, during 2005–2010. We also examined the effects of weekly minimum temperature, relative humidity and rainfall on the transmission of *P.vivax* and *P.falciparum* in this area. The results of the study showed that the primary cluster area included eight counties in western Yunnan along China–Myanmar border. Minimum temperature, relative humidity and rainfall were significantly associated with the transmission of *P.vivax* and *P.falciparum*, which provided detailed weekly information on the relationship between climatic factors and malaria transmission in the border area of Yunnan, China. These findings are vital for planning and implementing local malaria interventions, and contribute to strategy development for controlling and eliminating "border malaria" in Mekong river regional countries.(Cui *et al.* 2012)

5.4.1 Identified high risk area

Spatial clusters analysis can provide a public health tool for investigating high risk areas and clues for possible disease risk factors.(Clements *et al.* 2009) The identified malaria high risk area in this study, which located in the subtropical region along China–Myanmar border was consistent to the findings of previous studies.(Bi *et al;*. 2012; Clements *et al.* 2009; Hui *et al.* 2009) Malaria transmission in the border area of Yunnan has been an important issue in China due to the increasing malaria infections imported from neighbouring countries. The imported malaria cases are regarded to play a key role in initiating frequent outbreaks in Yunnan border.(Zhou *et al.* 2006;Zhu *et al.* 1994) Relatively high transmission mainly occurs in this bordering region compared to other provinces in China.(Yang *et al.* 2012) Among three China–Myanmar, China–Laos and China–Vietnam border areas in Yunnan

Province, China-Myanmar has the longest border (1997 km), the highest annual parasite incidence rate (API, > 2.3%) and the highest proportion of *P.falciparum* reported in positive blood smears (33%).(Zhu *et al.* 1994) This bordering region is a stable *P.falciparum* transmission area.(Lin *et al.* 2009) The identified high risk area along China–Myanmar border in western Yunnan appeared to be the dominating source of *P.falciparum* imported to other 21 provinces among 23 provinces reporting malaria cases in mainland China.(Lin *et al.* 2009; Zhou *et al.* 2011a; Bi *et al.* 2012) Although *P.falciparum* contributed to a majority of the imported cases in China,(Zhou *et al.* 2006) the current study found that there were more *P.vivax* malaria cases than *P.falciparum* malaria cases along China–Myanmar border, with the ratio of *P.vivax* to *P.falciparum* being 2.4:1 (19,106:7,946). The results were contrary to the situation along Thailand–Myanmar border where *P.falciparum* was a dominant malaria species.(Zhou *et al.* 2005) Thus, the local policy for malaria intervention should prioritise both parasites for bordering areas in Mekong river regional countries.

5.4.2 Estimated effects of temperature and relative humidity on malaria

Both temperature and relative humidity are considered environmental risk factors for malaria transmission.(Yang *et al.* 2012) In this study, significant associations between minimum temperature and the number of malaria cases appeared at a lag of 4 weeks, and up to 9 weeks for both types of malaria parasites after adjusting for relative humidity. An effect of maximum temperature for a lag of 3 weeks on *P.vivax* was reported in a temperate area in the Republic of Korea (ROK).(Kim *et al.* 2012) Other previous studies used monthly data and found that a significant association between minimum temperature and malaria transmission at a lag of one to two months.(Loevinsohn 1994; Bi *et al.* 2003; Tian *et al.* 2008) Temperature plays a crucial role in the transmission cycle of malaria parasite and mosquito survival.(Brooker *et al.* 2004) Studies found that at the temperature of 22 °C, a life cycle of malaria parasite development in mosquito vector is completed less than 3 weeks.(Bayoh *et al.* 2003; Njuguna *et al.* 2009; Teklehaimanot *et al.* 2004) If the humidity remains between 55% and 80%, it takes 15–25 days for *P.vivax* vector to complete its life cycle when temperature varies from 15–20 °C, and 20–30 days for *P.falciparum* vector to complete its life cycle if the temperature varies between 20–25°C.(Bhattacharya *et al.* 2006) In the study area, the lag effect started from week four and lasted to week nine, with a minimum temperature range of 11–16 °C, which is consistent with the time required for development of vector mosquito and for completion of the parasite life cycle in the local vector mosquito. An outbreak of the infection could therefore be predicted from climate forecasts, allowing early warning to be given. A climate-based early warning system could be used in this area to alert the authorities of possible changes in the risk level, either immediately or in the near future and to take an action to protect the vulnerable members of the population.

Relative humidity seems to have an indirect effect on not only the development of parasites but also the activity and survival of *anopheline* mosquitoes.(Dale *et al.* 2005) Relative humidity has been found to be one of the key determinants for the transmission of malaria, with low humidity observed to limit the distribution and abundance of mosquito vector in China.(Yang *et al.* 2010) A recent study of the impacts of climate change on malaria in China classified three malaria transmission zones based on monthly temperature and relative humidity changes, with Yunnan found to be located in a high risk zone of malaria transmission.(Yang *et al.* 2012) Our study identified a hot spot of malaria transmission in this high risk zone and narrowed it down to a local county scope. According to our estimates, the minimum temperature and humidity have significant effects on malaria, with the range of relative risk from 1.02 to 1.03 on *P.vivax*, and from 1.04 to 1.07 on *P.falciparum* for a 1 °C increase in minimum temperature, and from 1.02 to 1.04 on *P.vivax*, for a 10% increase in relative humidity. An association between relative humidity and *P.falciparum* was not found in this subtropical area, which is consistent with a previous study carried out in a tropical rain forest area along China–Laos border in southern Yunnan.(Tian *et al.* 2008) This may be due to the fact that the majority of *P.falciparum* cases are imported infections from neighbouring countries.(Zhou *et al.* 2006) There were different effects of relative humidity on *P.vivax* and *P.falciparum* in this study area. Significant effects of relative humidity on *P.vivax* reveal that relative humidity is one of key determinants on the transmission of *P.vivax* malaria. But non-significant effects of relative humidity on *P.falciparum* mean that it is probably not a limiting factor for *P.falciparum* malaria in this area. These findings provide important information for early intervention initiatives and in developing strategies for local malaria surveillance–response systems.

5.4.3 Estimated effects of rainfall on malaria

Rainfall is considered to be the predominant climatic factor on the transmission of malaria.(Bomblies *et al.* 2009) Rainfall is found to have a great influence on the completion of the life cycle of malaria parasite(Jusot *et al.* 2011) and it modifies the effects of temperature and increases the effects of humidity.(Yang *et al.* 2010) However, the influence of rainfall on malaria transmission is complex. Our results show different lag effects of rainfall on *P.vivax* and *P.falciparum*, which provide an example to explain to some extent such a complex inter-relationship. Two stages of the lag effects were examined, with a short lag of 2–4 weeks and a long lag of 9–10 weeks for *P.vivax,* and a short lag of 2–4 weeks for *P.falciparum*. This pattern in effect may be due to rainfall increasing breeding sites for vector mosquitoes such as pools of water, with a short lag effect of 2–4 weeks supporting this hypothesis. By contrast, heavy rainfall may destroy existing breeding places, interrupt the development of mosquito eggs or larvae, or flush the eggs or larvae out of the pools.(Tian *et al.* 2008) Therefore, it will take longer time to rebuild the mosquito life cycle for an infection. In addition, evaporation of pools keeps relative humidity at a high level which prolongs longevity of vector mosquitoes, and may have resulted in the long lag effect of 9–10 weeks for *P.vivax*. A long lag effect on *P.falciparum* was not observed in our study. The reason could be that overseas-imported *P.falciparum* has begun to dominate and other factors (e.g. life cycle of parasite, parasite adaptation, mosquito habits, etc) might be different from *P.vivax*. Further research on this issue needs to be warranted in the future.

5.5 Strengths and limitations

There are three strengths in this study. Firstly, this is the first study to assess the relationship between climatic factors and malaria transmission in the China–Myanmar border. Secondly, we obtained daily data of *P.vivax* and *P.falciparum* malaria cases, and daily weather data at a county level in Yunnan Province, China. This facilitated a detailed local assessment. Thirdly, we applied a DLNM to examine the weekly exposure–response relationship and its distributed lag effects(Gasparrini *et al.* 2010) on two types of malaria parasite. These results provide valuable information for both local health authorities and neighboring countries.

Two limitations of this study should also be noted. Firstly, we only examined the effects of climatic variables on malaria transmission, but non-climatic factors, such as human activities, socioeconomic status, vector control programs, drug resistance and environmental changes, may also affect the spread of this disease.(Lindsay *et al.* 1998; Githeko *et al.* 2000; Reiter 2001; Trape 2001) However, these non-climatic factors are unlikely to vary significantly on a weekly scale and unavailable for this research. Secondly, an investigation carried out in 2001 suggested that the under-reported malaria cases were five times higher than the actual number of reported cases in Yunnan.(Zhang *et al.* 2004) The underestimates of the true number of malaria cases is inevitable in our study.

5.6 Conclusions

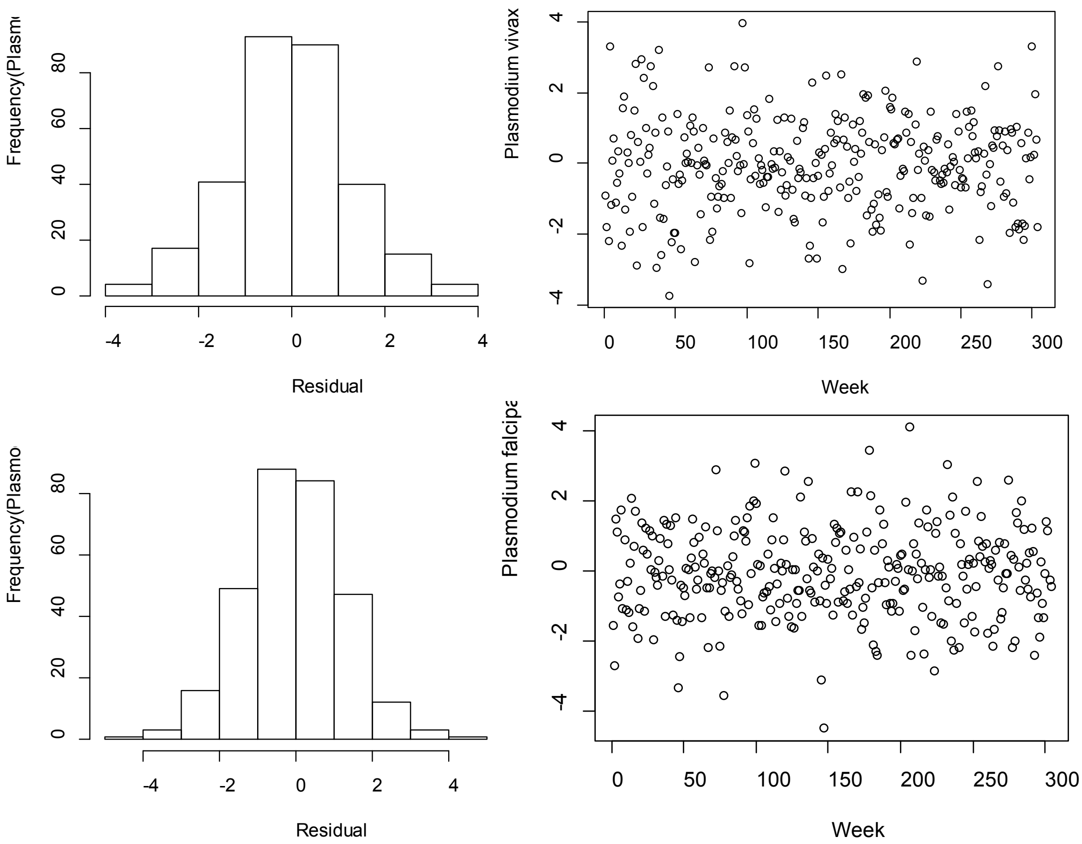
In summary, a high risk area of malaria transmission was identified along China–Myanmar subtropical region in Yunnan Province. The number of malaria cases in this high risk border area is likely to depend on temperature, relative humidity and rainfall. The estimated lag effects for the association between temperature and malaria are consistent with the life cycle of malaria parasite in mosquito vector. The results of this study will be useful for malaria surveillance-response systems in the Mekong river region. These findings may also be applicable to countries with a similar problem of malaria transmission.

Appendix 5.1

A.1 Checking the residuals for the temperature–malaria model

A.1 (a) Histogram of residuals

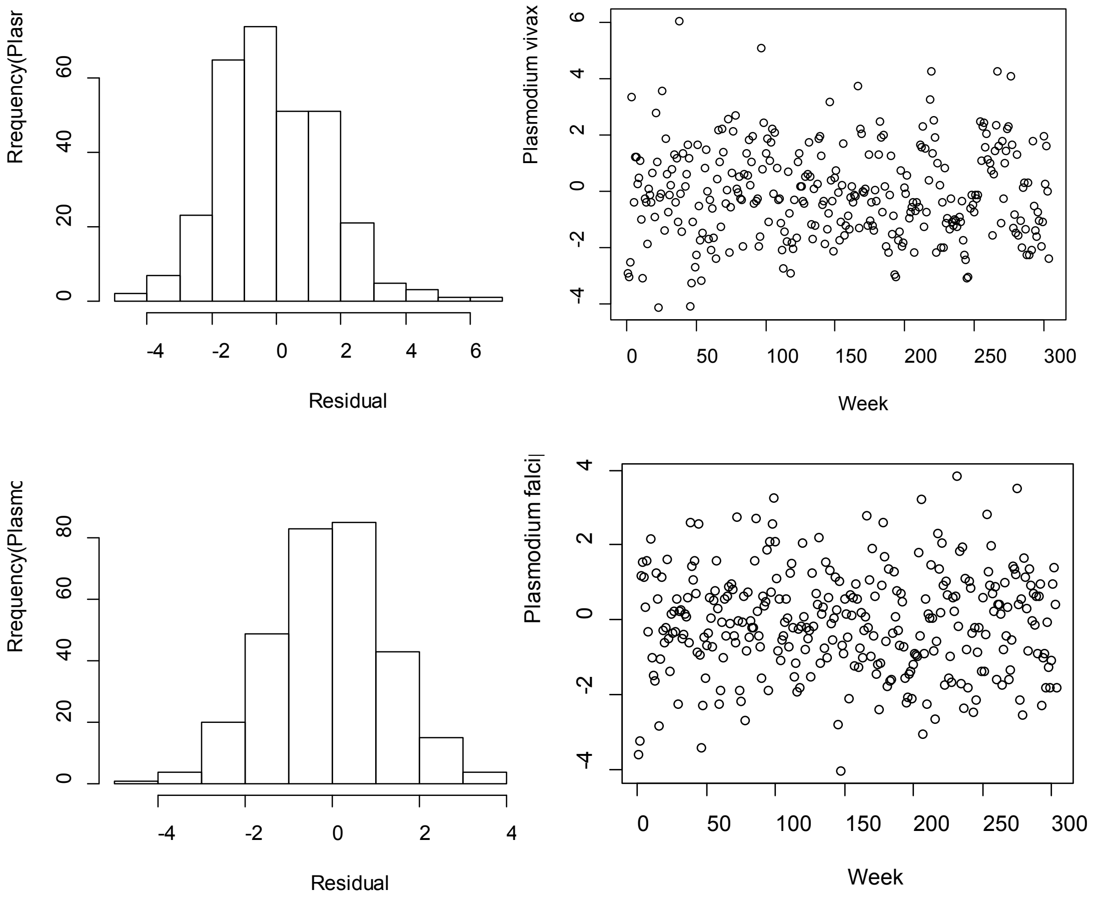
A.1 (b) Scatter plot of residuals over time



A.2 Checking the residuals for the rainfall–malaria model

A.2 (a) Histogram of residuals

A.2 (b) Scatter plot of residuals over time



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Chapter 6: **Can slides positivity rates predict malaria transmission?**

Citation

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YB was the principal author of the manuscript. YB, WH and ST initiated the study. YB, WH and YG designed the study and directed its implementation, including data analysis and interpreting. HL, YX, SC, LZ and YB performed field data collection. ST supervised the study and YB drafted the manuscript. All authors contributed to the manuscript edit, review and revising, and approved the final version of the manuscript.

Abstract

Background

Malaria is a significant threat to population health in the border areas of Yunnan Province, China. How to accurately measure malaria transmission is an important issue. This study aimed to examine the role of slide positivity rates (SPR) in malaria transmission in Mengla County, Yunnan Province, China.

Methods

Data on annual malaria cases, SPR and socio-economic factors for the period of 1993 to 2008 were obtained from the Center for Disease Control and Prevention (CDC) and the Bureau of Statistics, Mengla, China. Multiple linear regression models were conducted to evaluate the relationship between socio-ecologic factors and malaria incidence.

Results

The results show that SPR was significantly positively associated with the malaria incidence rates. The SPR (β = 1.244, $p = 0.000$) alone and combination (SPR, β = 1.326, $p < 0.001$) with other predictors can explain about 85% and 95% of variation in malaria transmission, respectively. Every 1% increase in SPR corresponded to an increase of 1.76/100,000 in malaria incidence rates.

Conclusion

SPR is a strong predictor of malaria transmission, and can be used to improve the planning and implementation of malaria elimination programmes in Mengla and other similar locations. SPR might also be a useful indicator of malaria early warning systems in China.

Key words

Malaria transmission, slide positivity rates, malaria elimination, international border areas, China

6.1 Introduction

Malaria is one of the major public health problems in China, especially in Yunnan Province, which has significant mortality, morbidity and economic burden. Yunnan Province is a malarial hyper-endemic area and had the highest number of malaria cases and deaths for more than 10 years until 2005 in China (Zhou *et al.* 2006; Zhu *et al.* 1994). The outbreaks of malaria happen annually along border areas in Yunnan, China. The likelihood of imported malaria cases has been increased along the border areas between Yunnan and Myanmar, Laos and Vietnam over recent years, due to increased trade and tourism in these areas (Zhou *et al.* 2009; Zhu *et al.* 1994). In order to control malaria it is important to enhance disease surveillance and evaluation of malaria transmission (The malEra Consultative Group on Monitoring Evaluation Surveillance, 2011a, 2011b) in this endemic region.

The intensity of malaria transmission can be estimated using different indicators such as annual blood examination rate (ABER), annual parasite index (API), slide positivity rate (SPR) and the incidence of malaria (Jensen *et al.* 2009; Metzger *et al.* 2009; Montanari *et al.* 2001; Roberts *et al.* 1997; Subbarao *et al.* 1988). In China, the annual malaria incidence is commonly used. Malaria incidence includes numbers of laboratory-confirmed malaria cases and other cases diagnosed with clinic symptoms (e.g. fever) as a numerator and the local population as a denominator. The local population size might be under- or overestimate because census is only carried out once 10 years in China. Huge population movement is common due to economic development in China in the last three decades. Thus, malaria incidence might be inaccurate due to limited health care resources (Jensen *et al.* 2009) or under- or overestimates of population size (Hay *et al.* 2004). It is important to estimate the burden of malaria accurately for planning public health interventions. Slide positivity rate (SPR) has been used as a surrogate to measure the incidence of malaria (Jensen *et al.* 2009; Lee *et al*. 2010; Roy *et al*. 2011; Subbarao *et al*. 1988), to define the level of malaria endemicity (Hay *et al*. 2004), and to identify malaria high risk areas (Joshi *et al.* 1997). This is a principal monitoring indicator in the malaria elimination programme in China for the period 2010 and 2020 and it has been monitored since the 1980s (China Department of Disease Control 2010; China National Malaria Office of Global Fund 2003) through the malaria annual reporting system. The changes in malaria incidence can be estimated from the SPR trends (Jensen *et al.*, 2009). Some studies have demonstrated that SPR has steadily decreased with the decline in malaria incidence (Lee *et al.* 2010), while others found that the annual parasite index (API) increased, but SPR kept steady at the same level over 20 years (Metzger *et al.* 2009).

The development of the malaria early warning system (MEWS) has been started based on the surveillance system in China over recent years (Wen *et al.* 2006; Yang *et al.* 2002). However, these studies are limited to climatic indicators and did not take advantage of monitoring indicators, which can help improve malaria prevention and control, especially in the early stage of malaria elimination. Moreover, the relationship between SPR and the incidence of malaria is not clear in the border areas of Yunnan Province, China. This study aimed to examine the role of SPR in monitoring malaria transmission, and improve the planning and implementation of malaria control and prevention programmes.

6.2 Methods

6.2.1 Study area

Mengla County is in south Yunnan Province and ranges from 21° 09' to 22° 24'N, 101° 05' to 101° 50'E, bordering Myanmar to the west and Laos to the east, south and south-west as well as other counties of Yunnan Province to the north (Figure 6.1). It has an area of 7,093 sq km with an international border of 740.8 km. Mengla County includes 10 townships and four farms with a population of 0.2 million. Its elevation ranges from 480 m to 2,023 m. It is a high malaria transmission region. Malaria has been the top infectious disease for decades and was ranked the first (accounted for 46.7% of total cases) in all infectious diseases in 2003. Mengla was ranked top six for its annual malaria incidence (400.4/100,000) among the 2,353 counties of China during 1994-1998 (Gao *et al.* 2003). Malaria becomes one of the major public health problems in this region. Increased travel across international border (China-Myanmar and China-Laos) aggravates the burden of malaria (Hu *et al.* 1998; Zhu *et al.* 1994). In the national malaria elimination programme of China launched in 2010, Mengla was identified as one of the 75 first line counties in China and will achieve the goal of no indigenous malaria cases by 2017 and malaria elimination by 2020 (China Department of Disease Control 2010).

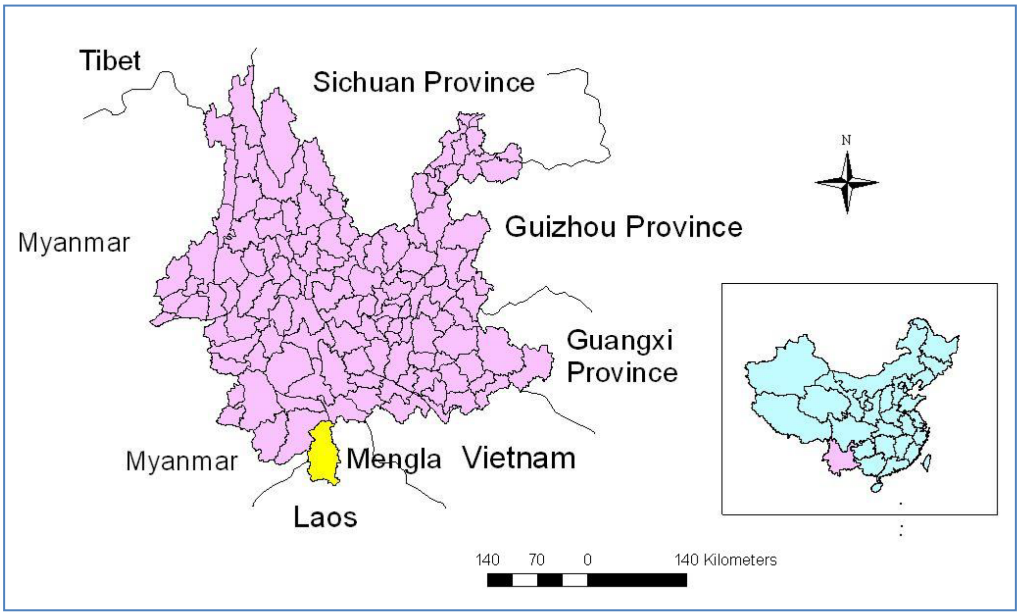

Figure 6.1 The location of Mengla County, Yunnan Province, China.

6.2.2 Data collection

Data on annual malaria cases and SPR in all fever patients were obtained between 1993 and 2008 from the malaria annual reporting system in the Mengla Center for Disease Control and Prevention (CDC), China. Mengla is one of the sentinel counties selected for both national and provincial malaria surveillance, and has kept good records for malaria. The dominant species of parasite is *Plasmodium vivax*, but *Plasmodium falciparum* infections also exist in this county. The ratio of *P. vivax* to *P. falciparum* cases was 4:1 (Tian *et al.* 2008). Both species were combined in this study. SPR defined as the number of laboratory-confirmed positive slides examined per 100 slides, expressed as a percentage (Jensen *et al.* 2009; Montanari *et al.* 2001). The calculation of SPR is

SPR for a year = (number of positive slides / total slides examined) × 100

Blood smears of febrile patients were examined, and confirmed by microscope and/or by rapid diagnostic test.

Data on climatic variables (including annual average relative humidity, mean maximum temperature (Tmax), mean minimum temperature (Tmin) and rainfall); and the annual average income per capita of farmers and the population size of this county for the same period were retrieved from the Mengla Bureau of Meteorology and the Mengla Bureau of Statistics, respectively.

6.2.3 Data analysis

Spearman's correlation analyses were conducted to evaluate the correlations between SPR and the incidence of malaria, as well as other independent variables. Six step-wise multiple linear regression models were employed to examine the effects of SPR on malaria transmission after adjusting for confounding variables. Square root transformation was applied to the malaria incidence to assure the normality to satisfy the assumption of linear regression analysis. The Durbin-Watson (DW) statistic was used to detect the presence of autocorrelation (a relationship between values separated from each other) in the residuals (prediction errors) from the above regression analysis. If the DW statistic is substantially equal to two, it indicates no autocorrelation. Akaike Information Criterion (AIC) was used to select the most suitable model. All data analyses were conducted using SPSS for WinWrap Basic (PASW Statistics, Version 18).

6.3 Results

Figure 6.2 shows the annual pattern of malaria incidence and SPR in Mengla County. In this hyper-endemic region, a total of 8,962 malaria cases were reported and annual malaria incidence rates ranged from 23 to 648 per 100,000, while the SPR varied between 0.42% and 13.08% from 1993 to 2008. The scatter plot with regression line depicts the crude relationships between incidence rates of malaria and SPR (Figure 6.3). The plot reveals that incidence rates of malaria were positively associated with SPR.

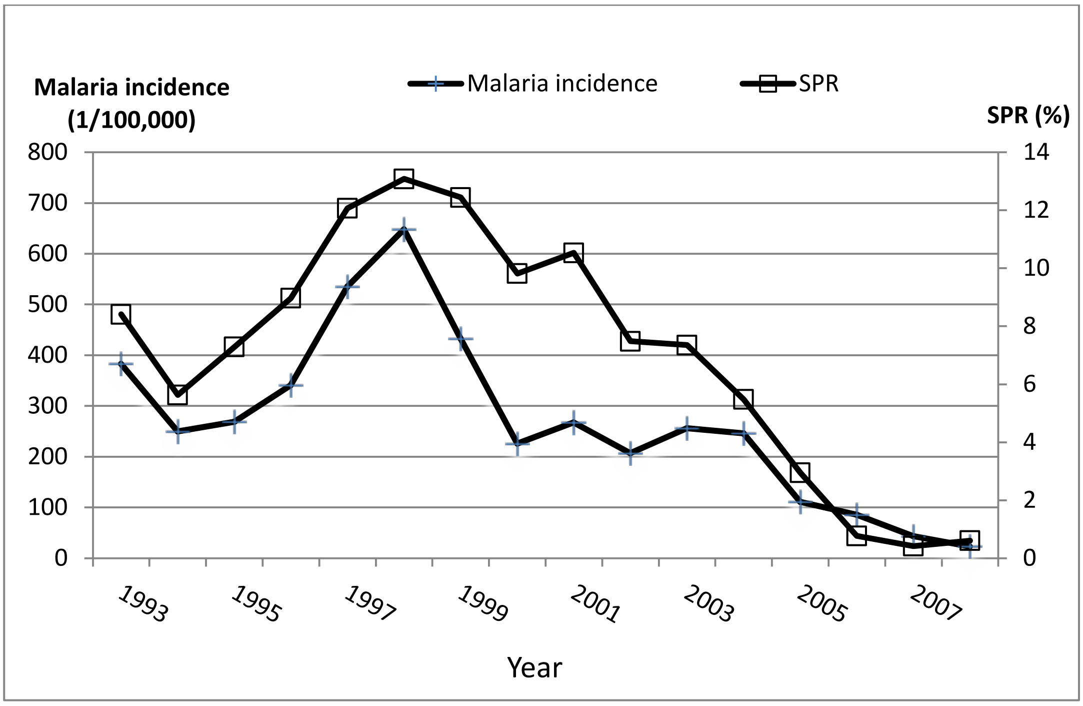

Figure 6.2 Malaria incidence and slide positivity rates (SPR) in Mengla County, China, 1993-2008

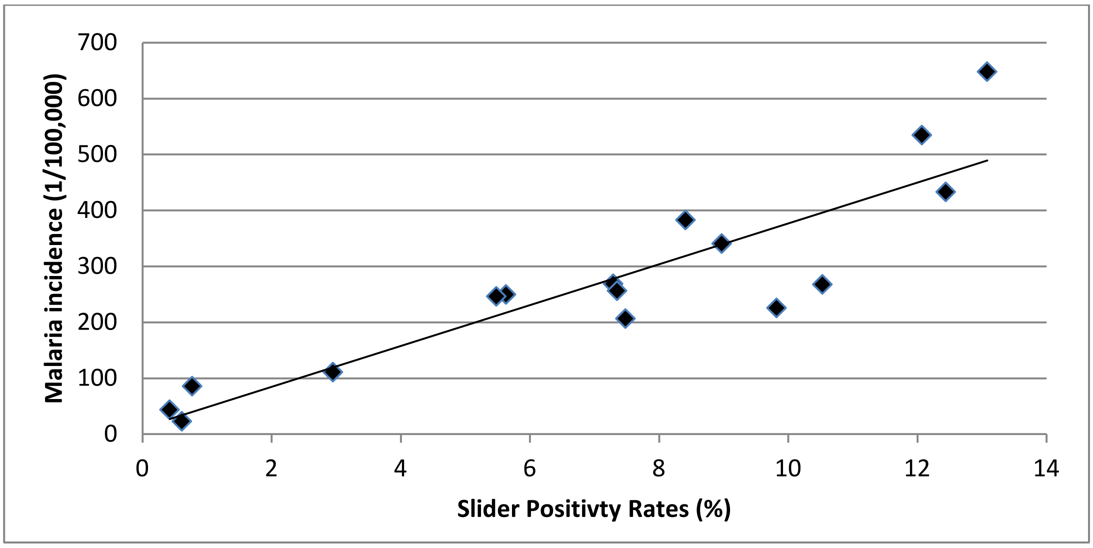

Figure 6.3 The relationship between slide positivity rates and crude malaria incidence in Mengla

Spearman correlations between malaria incidence and socio-environment variables show (table 6.1) that SPR ($r = 0.85$, $p < 0.01$), income ($r = -0.76$, $p < 0.01$) and humidity ($r = 0.57$, $p < 0.05$) were statistically significantly associated with malaria incidence. However, there was no significant association between other climatic variables and annual malaria incidence.

Table 6.1 Spearman correlations between malaria incidence and social and climatic variables, 1993-2008

Variables	SPR	Income	Tmax	Tmin	Rainfall	Humidity
Income	-.544*					
Tmax	-0.38	0.26				
Tmin	-0.04	0.39	0.27			
Rainfall	0.15	-0.35	-0.45	-0.41		
Humidity	.792**	-.567*	-.515*	-0.22	0.39	
Malaria incidence	.853**	-.756**	-0.23	-0.20	0.10	.568*

* $p < 0.05$ ** $p < 0.01$

SPR Slide positivity rates, *Tmax* Maximum temperature, *Tmin* Minimum temperature

Six models have been used to evaluate the association between malaria incidence and predictors (Table 6.2). Model 1 shows SPR ($\beta = 1.244$, $p = 0.000$) alone can explain as high as 85% of the variation in the response variable. This provides strong evidence that SPR is a very good surrogate measure for the malaria incidence rates. Models 2 - 6 show that the inclusion of the additional covariates of Tmax, income and humidity moderately improved the model fit with the increase of adjusted R^2 (88-95%) and DW value (0.57-2.11), and decrease of AIC (75.93-65.62) in these models. Model 6 (R^2: 0.951, AIC: 65.62) is chosen as the optimal model due to its best goodness-of-fit of the data. In summary, the best fitting model includes SPR, income, maximum temperature and humidity as the predicting variables for the annual malaria incidence.

Table 6.2 Association between malaria incidence and SPR in Mengla, China 1993-2008

Models	**SPR**			**Adjusted**	**AIC**	**D-W(p-value)**
	β	**S.E.**	**P**	**R^2**		
Model 1	1.244	0.133	0.000	0.851	75.93	0.78 (=0.001)
Model 2	1.359	0.128	0.000	0.884	74.36	0.57(<0.001)
Model 3	1.039	0.137	0.000	0.895	72.79	1.12(=0.005)
Model 4	1.152	0.110	0.000	0.939	67.32	1.21(=0.007)
Model 5	1.318	0.163	0.000	0.924	70.67	1.54(=0.045)
Model 6	1.326	0.131	0.000	0.951	65.62	2.11(=0.246)

SPR: Slide positivity rates; D-W: Durbin-Watson; AIC: Akaike Information Criterion; Model 1: SPR; Model 2: SPR + Tmax; Model 3: SPR+ income; Model 4: SPR+Tmax+income; Model 5: SPR+Tmax+humidity; Model 6: SPR+ Tmax + income +humidity.

Table 6.3 displays crude and adjusted results from linear regression analyses. In crude models, four predictors were tested individually. Their adjusted R^2 were -3.2% (Tmax), 45% (humidity), 47% (income) and 85% (SPR), respectively. In the multi-variable models, without SPR, only 54% of variation of malaria incidence was accounted for by the other three independent predictors (Tmax, humidity and income), whereas 95% of variation of the malaria incidence was explained after SPR was added to the model.

Table 6.3 also shows that SPR (β = 1.326, p < 0.001) is a significantly independent predictor of malaria incidence after adjustment for Tmax, humidity and income. Keeping other independent variables constant, every 1% increase in SPR corresponds to an increase of 1.76/100,000 (the squared malaria incidence) in malaria incidence rates.

Table 6.3 Regression coefficients of the best model

	Crude				Adjusted					
					Without SPR			With SPR		
Variables	**β**	**S.E.**	**P**	**Adjusted R^2**	**β**	**S.E.**	**P**	**β**	**S.E.**	**P**
Tmax	-2.57	3.522	0.479	-0.032	2.25	2.717	0.424	2.43	0.883	0.019
Humidity	2.15	0.589	0.003	0.450	1.56	0.777	0.068	-0.68	0.335	0.069
Income	-0.01	0.002	0.002	0.469	0.004	0.002	0.081	-0.003	0.001	0.001
SPR	1.24	0.133	0.000	0.851				1.326	0.131	0.000
Adjusted R^2						0.536			0.951	

Multiple linear regression model: SPR+Tmax+humidity+income (model 6)

Figure 6.4 shows the results of the regressive forecast chart in which figure 6.4-A included SPR and figure 6.4-B did not. Figure 6.4-A indicates that the predicted and the observed value of annual squared root malaria incidence rates matched well. The incidence rates in 1999, and in 2003, were theoretically predicted by the model and validated by the observed values. However, for figure 6.4-B the predicted and the observed value of the malaria incidence cannot be matched well, especially in year 1997-98. The observed values of these two years are out of the confidence interval. There is a wider confidence interval in figure 4-B than in 4-A. All results stated that the regressive forecast of annual malaria incidence with SPR is more accurate than that without SPR in Mengla County over the study period.

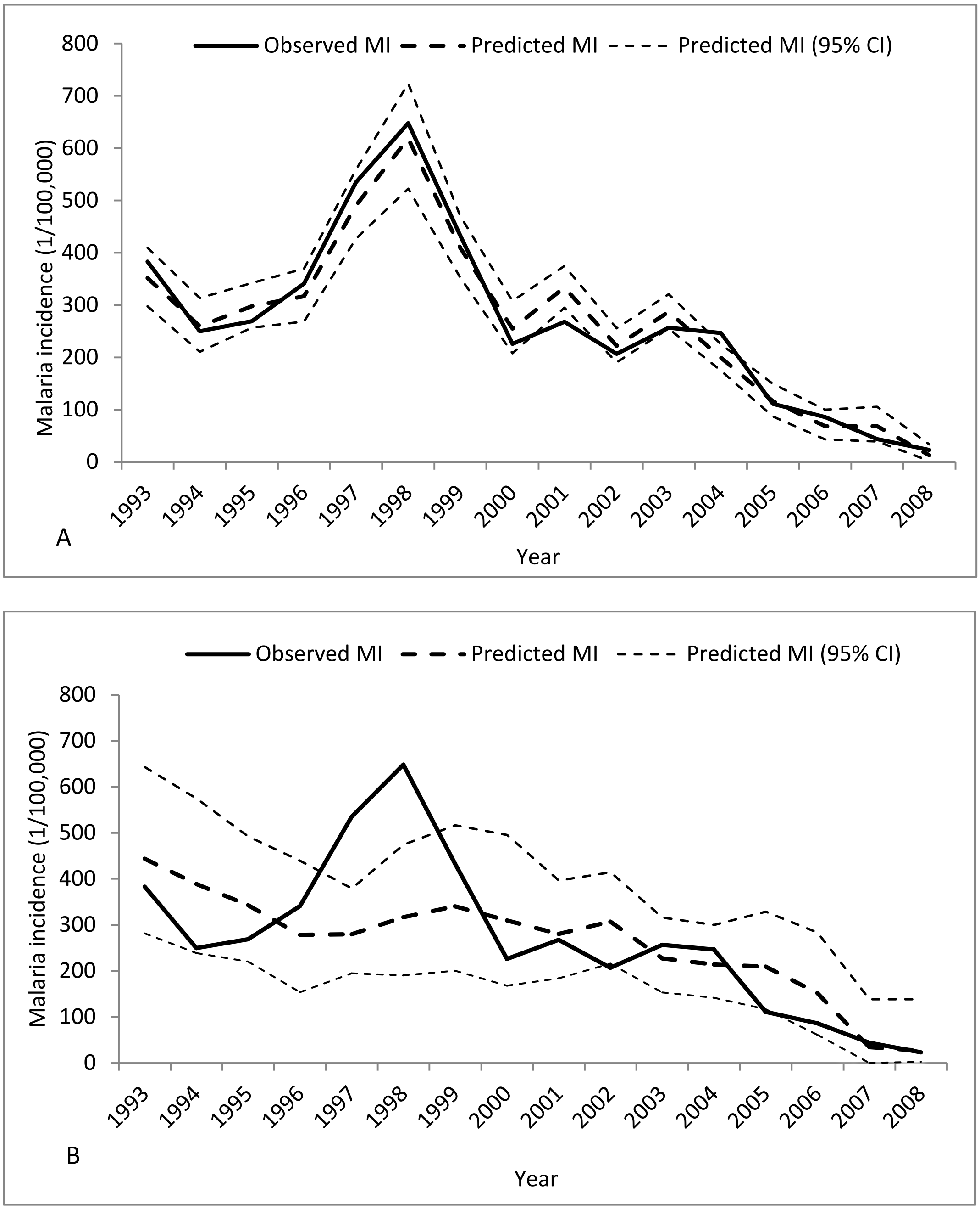

Figure 6.4 Regressive forecasts of annual malaria incidence in Mengla, China, 1993–2008

(The results based on Model 6, (A) included SPR, (B) did not include SPR)

6.4 Discussion

SPR varied between 5.48% and 13.98% from 1993 to 2004 in Mengla. SPR under 2.9% is considered the absence of indigenous transmission (Subbarao *et al.* 1988). Evidently, there is indigenous malaria transmission in Mengla (Hu *et al.* 1998; Zhu *et al.* 1994). Less than 5% of SPR is considered the transition from the control stage to the pre-elimination stage (Aregawiet *et al.* 2008) which implied that Mengla went through pre-elimination malaria after 2004. Five *Anophiline* species have been identified to be vectors of malaria in Yunnan Province (Bureau of Endemic Diseases Control of People's Republic of China 1998; Zhu *et al.* 1994). *Anopheles minimus* is the major vector in this endemic border area - Mengla (Hu *et al.*, 1998; Zhu *et al.*, 1994b).

SPR has been used as a surrogate of malaria incidence (Jensen *et al.* 2009; Lee *et al.* 2010; Subbarao *et al.* 1988). In Uganda, SPR provided a useful measure to estimate malaria incidence among children (Jensen *et al.* 2009). To measure malaria transmission at a pre-elimination stage, SPR was used as an indicator to evaluate a malaria control programme on the island of Principe (Lee *et al.* 2010). In current study, the decrease in SPR corresponded to the malaria incidence decline. This result is consistent with the result of other studies in which changes of SPR provided an alternative method for estimating changes in the incidence of malaria (Jensen *et al.* 2009; Lee *et al.* 2010). A downward trend in SPR in Mengla is in accordance with the decline of both *P.vivax* and *P. falciparum* malaria incidence in Yunnan (Clements *et al.* 2009b). After 2005, both SPR and malaria incidence sharply decreased in Mengla. This may be due to the impact of the Mekong Roll Back Malaria program (2002-2004) and the Global Fund (Round one) between 2003 and

2008, especially with the free treatment for malaria infection financed by the Global Fund in Mengla County since 2005.

Malaria transmission is greatly affected by socioeconomic conditions (Brooker *et al.* 2004; McMichael *et al.* 2006). Low-middle income was significantly associated with malaria transmission in Indonesia (Dale *et al.* 2005). The disappearance of malaria in some areas of Europe was associated with economic development (Ijumba *et al.* 2001). In this study, income was negatively associated with malaria incidence. The decrease in malaria incidence was consistent with the increase in income. This can be explained by the development of the general economy in Mengla County in the last two decades. Mengla is a poor region. Twenty-six ethnic minority groups accounted for 72% of the total population, and approximately 96% of Mengla is mountainous. The main income is from rice, rubber, cane sugar and tea (it is the place of origin of Pu Er tea) (Encyclopedia of Baidu). The local economy has been improved since the 1990s by planting rubber trees, tropical fruit trees, tea, and an increase in trade with Laos, Myanmar and other Mekong-river region countries. The incomes of farmers have gradually increased, which has led to better living conditions and improvements in sanitation and health. These improved socio-economic conditions may be one of the key reasons for the decreased malaria pattern in this region. Further investigation of the association between socioeconomic conditions and malaria transmission is warranted in this endemic area.

In this study, relative humidity has a significant positive association with malaria incidence. Relative humidity appears to have an effect on malaria transmission indirectly, as humidity may affect the development of the parasite, and the activity and survival of anopheline mosquitoes (Dale *et al.* 2005). More humid and hotter than usual conditions may increase *anopheline* survival, thus resulting in an increase in outbreaks of malaria (Zucker 1996). However, low humidity could reduce the numbers of the mature mosquitoes (Keiser *et al.* 2002), therefore resulting in no malaria transmission (Dale *et al.* 2005). As a tropical rain forest area situated just south of the Tropic of Cancer, Mengla has wet and hot weather, which provides mosquitoes with favourable breeding sites.

Temperature has an important effect on the transmission cycle of the malaria parasite and mosquito survival (Brooker *et al.* 2004; Martens *et al.* 1995). Temperature is considered to play a crucial role in malaria transmission, which was identified by other studies (Bi *et al.* 2003; Clements *et al.* 2009; Kleinschmidt *et al.* 2001; Lindsay *et al.* 1996; Zhou *et al.* 2005) and is reported to be a predictor of malaria transmission. In a previous study in 2008, a positive association between minimum temperature, maximum temperature and malaria incidence based on monthly time series data was found in Mengla County (Tian *et al.* 2008a). However, the association between temperature and malaria incidence was not observed in current study. This may because annual weather variables are used for analysis. In multiple linear regression analysis, however, maximum temperature became a significant predictor of malaria transmission after adjustment for other factors. Maximum temperature and another three predictor factors together explained 95% of variance of malaria incidence.

Malaria transmission is influenced by various factors including climatic (Berrang-Ford *et al.* 2009; Roll Back Malaria Cabinet Project 2001) and non-climatic factors

(Githeko *et al.* 2000; Lindsay *et al.* 1998; Reiter 2001).The spatial and seasonal distribution of malaria is largely determined by climate (Tanser *et al.* 2003), and climatic factors (e.g. rainfall, temperature and humidity) have been widely used and recognized in the MEWS (Hay *et al.* 2003; Thomson *et al.* 2006). However, climatic factors are not enough for MEWS, which requires comprehensive and integrated indicators. To predict the timing and severity of malaria epidemics in MEWS, epidemiological surveillance indicators (for example SPR) should be considered (Ceccato *et al.* 2005; Thomson *et al.* 2001). Blood examination of parasite appearance is a key indicator in the early detection of malaria transmission and it is compulsorily reported in China. The use of SPR can obviously assist the development of MEWS in malaria elimination program in China. It can also be used to evaluate the malaria surveillance systems in China.

This study has several strengths. Firstly, this is the first study to examine the role of SPR in monitoring malaria transmission at a county level in China. Secondly, the model developed fitted the data quite well. The SPR alone, and combination with other predictors can explain 85% and 95% of variation in malaria transmission, respectively. Finally, the results of this study may help plan and implement malaria control and prevention interventions in the field.

The limitations of this study should also be acknowledged. Firstly, SPR and income were collected annually, and we were unable to examine the seasonal pattern of malaria transmission and conduct any finer analyses (e.g. monthly). Secondly, some other factors (e.g. mosquito density, movement of the people across the border and vegetation coverage) may play a role in the transmission of malaria. Because of the lack of the data, these factors were not adjusted for in the model. Thirdly, a 16-year small sample was used in this study. If the latest data can be included, the results will be more convinced. Finally, the data for this study were only collected from Mengla, Yunnan Province. We didn't have detailed information on *P.vivax* and *P. falciparum,* and the recurrence of *P.vivax* infection was also not considered. So we couldn't analyse them separately. Thus, caution is needed when the findings of this study are generalized to other locations.

6.5 Conclusions

In conclusion, SPR was significantly associated with malaria incidence and identified as a strong predictor of malaria transmission in Mengla County. The results of this study support the use of SPR. The multi-variable regression model developed in this study may have implications for the global malaria elimination campaign. The improved understanding of the relationship between SPR and malaria transmission will assist in the establishment of a malaria early-warning system to predict this wide spread disease in endemic areas.

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Chapter 7: **General Discussion**

7.1 Overview

It is recognized that a variety of factors influence the transmission of malaria. The assessment of spatial and temporal patterns of malaria can provide important information on where and when public health interventions should be carried out. Malaria is endemic in Yunnan Province and a better understanding of malaria transmission patterns and their determinants is vital for developing effective malaria surveillance–response strategies in Yunnan Province, China. This study aimed to examine spatial and temporal distribution of malaria in Yunnan Province to identify the high risk areas of malaria infection and to assess the relationships between socio–ecologic factors and malaria at a county level. The different analytic techniques including spatial and time series analyses were used to achieve specific objectives: 1) to analyse and visualise the spatial and seasonal patterns of malaria infection; 2) to identify the high risk areas and periods of disease; 3) to assess the effects of risk factors on malaria transmission by developing spatio-temporal models.

The focus of this final chapter is to bring together the key findings from previous three results chapters to provide an overall picture of this study. Figure 7.1 shows the connection and major findings of this study. Each of the results chapters has its own discussion section in which the findings have been separately and specifically discussed in relation to the literature, strengths and limitations of the study, and implications for public health policy and practices. This chapter summarizes the overall findings from the three manuscripts and provides a general discussion.

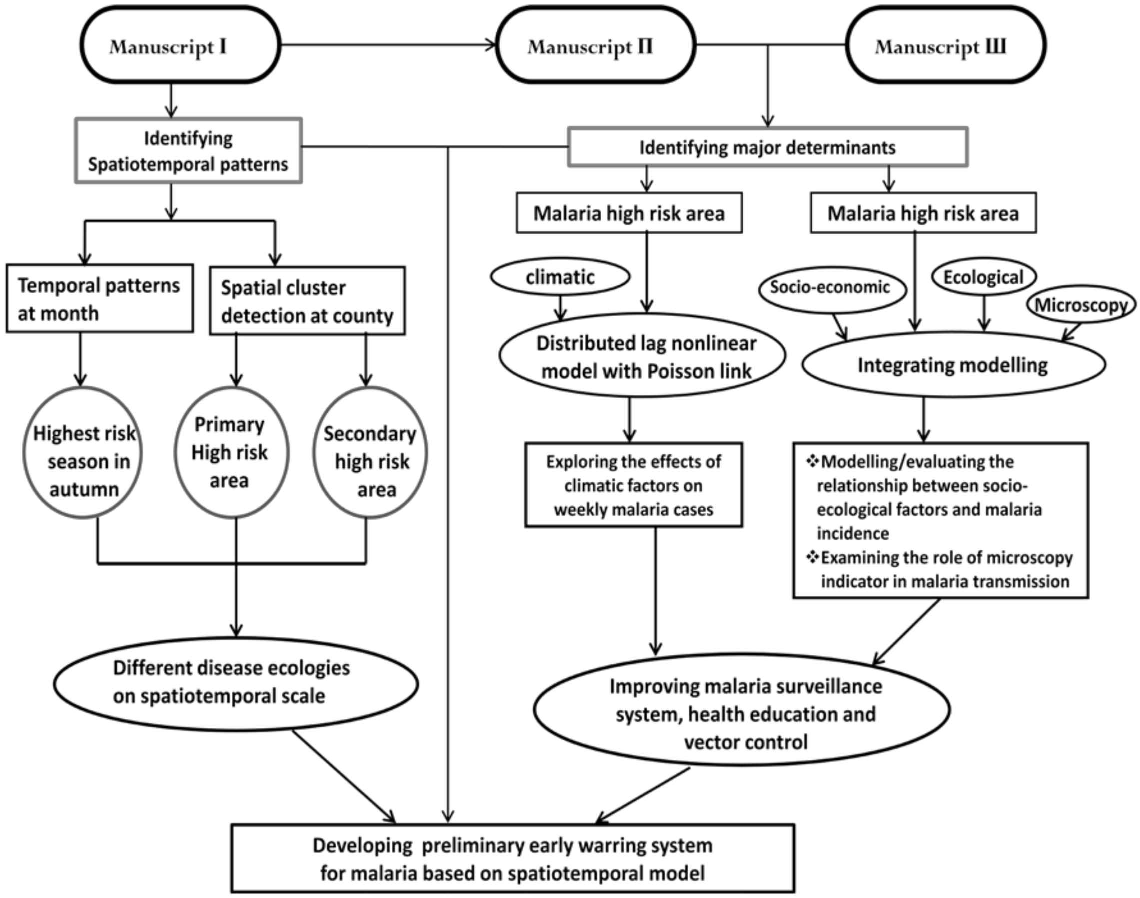

Figure 7.1 Framework of research in this thesis

7.2 Substantive discussion

The results of this study show that the incidence and mortality of malaria have decreased gradually and varied in space and time across Yunnan. Spatial clusters, seasonal patterns and geographic changes of malaria transmission were assessed, which suggests that the variation in both spatial and temporal distributions of malaria disease is driven by a complex set of socio-ecological factors. This study helps to identify socio–ecological determinants of malaria transmission in the high risk areas to assist disease surveillance and control programs.

The analysis of malaria epidemic patterns can uncover important information and GIS visualisation can enable the identification of spatial patterns for further investigation to explore risk factors of malaria transmission in specific locations. The results of this study show that both malaria incidence and mortality were not randomly distributed in Yunnan with the identification of the primary cluster area along the China-Myanmar border in western Yunnan and the secondary cluster area along the China-Laos and the China–Vietnam borders in southern Yunnan. There was decreased malaria mortality in eastern areas in Yunnan for the last two decades. The high risk cluster areas of malaria identified in this study were consistent with others' findings in Yunnan (Clements *et al.* 2009; Hui *et al.* 2009). The primary cluster area included eight counties and the concentration of malaria clusters has remained along the international border in the past two decades which demonstrates that there has been an increasing risk of imported malaria infections in Yunnan from the neighbouring countries. The main reason could be mass mobile population across the international border like tourism, labour workers output and trade. For example, there was an estimated over 10 million mobile population in the border area of Yunnan each year and this number keeps increasing (Xu *et al.* 1997; Hu *et al.* 1998).

The endemic malaria in Yunnan Province was recognized as a source to spread *P. falciparum* malaria to other provinces in the non-endemic area in China (Lin *et al.* 2009). The cluster areas of malaria transmission identified in this study could be the dominating source of *P. falciparum* malaria imported to other provinces of China. In this study, we found that the highest risk of malaria transmission occurred in autumn (June-August, RR = 58.91, $P < 0.001$) and followed by summer (September-November, RR = 31.91, $P < 0.001$) in Yunnan Province. The finding of malaria transmission peaks in autumn rather than summer is consistent with the studies in Africa (Mordecai *et al.* 2013). The results of this study showed that for all seasons, the geographic location of the primary cluster was identified along the China–Myanmar border. The high risk seasonal clusters (autumn and summer) have concentrated in 11 counties in this border area in western Yunnan for over 20 years (Figure 4.6), where malaria mortality (0.06–1.23/100,000) were 5–12 times higher than that of Yunnan Province (0.01–0.12/100,000). The same high risk seasons were found in Yunnan. Other studies also reported that the peak times of malaria incidence occurred in summer and autumn (Clements *et al.* 2009; Hui *et al.* 2009). This temporal pattern was probably related to the rainy season with 85% of rainfall between May and October in Yunnan, when farmers usually work in the field and even sleep outdoor. The lack of personal protection and failing of residual spraying facilitated malaria transmission (Sarah *et al.* 2008; Hui *et al.* 2009). Hence, the results of this study indicate that there was a remarkable variation in the spatial and temporal distribution of malaria transmission in Yunnan Province.

The results of analysis on socio-ecological determinants of malaria transmission reveal that there was a link between climatic, socio-ecological risk factors and malaria transmission in the border areas of Yunnan Province. Climatic factors are considered as important determinants of malaria transmission (Berrang-Ford *et al.* 2009). This study shows that temperature, relative humidity and rainfall were associated with malaria in Yunnan. Temperature was significantly associated with the number of weekly malaria cases and annual malaria incidence while relative humidity was associated with annual malaria incidence in Mengla County along the China–Laos border. The significant association between relative humidity and weekly *P.vivax* cases was observed, however a significant association between relative humidity and weekly *P.falciprum* case was not found in the primary cluster area along the China–Myanmar border. The reason for this may be due to the fact that the majority of *P.falciparum* cases were imported from Myanmar, and therefore relative humidity was probably not a major determinant of *P.falciparum* transmission in the China–Myanmar border area (Zhou *et al.* 2009). Rainfall was associated with both weekly *P.vivax and P.falciparum* cases in this study. This effect may be because rainfall can increase breeding sites and provide favourable conditions for mosquito larvae to reproduce and develop abundantly, which may increase the potential of malaria transmission. Socio-economic conditions greatly influence malaria transmission (McMichael *et al*. 2006). In this study, average income per capita of farmers was negatively associated with malaria incidence. Malaria incidence decreased with the increased income, which suggests that the income may directly/indirectly influence the incidence of malaria.

Time lags of climate could affect climate sensitivity diseases such as mosquito-borne diseases (Tong *et al.* 2001; Hu *et al.* 2010; Tian *et al.* 2008). It is important to consider the impact of climatic factors and understand their lag effects on malaria transmission. A study conducted in the East African highlands found that in time lag effects of 1–2 months and 2–5 months between monthly rainfall, maximum and minimum temperature were significantly correlated with monthly malaria incidences (Zhou *et al.* 2005). Other studies also reported that a lag effect of 1-2 months between monthly minimum, maximum and rainfall and malaria incidence were evident in Suchen county and Mengla county, China (Bi *et al.* 2003; Tian *et al.* 2009). The results of this study found that the lag effects of minimum temperature on weekly malaria cases appeared at a lag of 4 weeks and the effects persisted up to 9 weeks. Time lag effects of rainfall and relative humidity on weekly malaria were also significantly examined in this study. For instance, lags of 2–4 weeks and 9–10 weeks between weekly rainfall and weekly malaria cases, and 3–8 weeks between relative humidity and malaria were found in the China–Myanmar border in Yunnan Povince. Such delays are consistent with the development of mosquitoes and the incubation period of malaria parasite within mosquitoes and in a human host. At an average temperature of 20 ˚C, it requires about 28 days for the maturation of mosquito vector to complete its life cycle. At this temperature, malaria cases are expected to, therefore, appear 9–10 weeks after assuming an average incubation period in a human host at about 10–16 days (Teklehaimanot *et al.* 2004). The findings of such lag effects may assist malaria control officers to plan and implement effective public health interventions in advance.

In this study, we endeavoured to develop multi-variable regression models to evaluate the relationship between socio-ecological variables and malaria incidence in Mengla County along the China-Laos border. Six models were developed and the optimal model 6 ($\beta = 1.326$, $P < 0.001$), which included four independent variables (i.e. SPR, maximum temperature, income and humidity), was chosen to predict malaria incidence. We found that in the multi-factor models, if we entered SPR in the model, only 54% of variation of the malaria incidence was accounted for by other 3 independent predictors (maximum temperature, income and humidity), whereas, 95% of variation of the malaria incidence was explained after SPR was added to the model. In the manuscript Ш, we considered the epidemiological monitoring indicator (i.e. SPR) as a key indicator to be integrated with socio-ecological factors to predict the malaria incidence and recommend that SPR be used to assist the development of malaria early warning systems in China. We acknowledge that daily/weekly/monthly malaria cases provide a quicker data source than the seasonal/annual SPR for malaria early warning, but SPR is a microscopic indicator, which is more accurate than the malaria incidence to estimate the intensity of malaria transmission. SPR is reported from annual malaria surveillance system while malaria cases are reported from the national notifiable diseases surveillance system (NNDSS). We recommend that SPR be used to validate NNDSS and to improve the planning and implementation of malaria elimination programmes in Mengla and other similar locations.

The findings of this study suggest that changes in climate and environment may have direct and indirect impacts on the transmission of malaria. Climate and environmental factors can influence the life cycle of malaria parasite and mosquito survival and breeding sites. Additionally, these factors affect human behaviour and may determine the likelihood of human exposure to malaria.

7.3 Public health implications

The findings from this study may have a number of public health implications in the planning and development of malaria control and prevention policies as described below:

1. GIS and spatial analytical methodological approaches used in this study may be applicable in the surveillance of malaria and other mosquito-borne diseases to identify and monitor the high risk areas over different periods of time. For example, the application of SaTScan technique will effectively identify the high risk areas of the disease and GIS tool can be used to create visual maps of disease patterns which

will provide further information to assist identifying possible risk factors of disease transmission.

2. The findings of this study suggest that the pattern of malaria has varied spatially and temporally in Yunnan Province. The high risk area of disease was found along the international border and autumn was found as the highest risk season. The study provides important evidence on the spatial–temporal pattern of malaria so that public health authorities can target high risk areas and develop most effective public health intervention strategies, to protect vulnerable groups. For instance, increasing insecticide spraying in high-risk areas during disease epidemic seasons and decreasing it during low-risk seasons will improve the cost-effectiveness of the operations.

3. The study examined significant relationships between climatic, socio–economic and ecologic factors and malaria risk in Yunnan Province. The integration of climatic, socio-economic and ecological datasets may provide valuable information for the development of epidemic forecasting models. These efforts, if successful, may have significant implications for disease control decision-making process and can assist public health professionals to determine public health priorities and use resources more efficiently and effectively.

4. Computer models need to be developed on the basis of these findings to alert the health authorities of possible changes in the risk level under different socio-environmental conditions, either immediately or in the near future. An early warning system needs to be established to assist disease surveillance and risk management

programs. Thus, health education, vector control and other intervention programs could focus on high risk communities before outbreaks occur.

5. The methods used in this study may also have implications for other vector-borne diseases, e.g. dengue fever, also for countries with a similar situation of malaria transmission.

7.4 Strengths of the study

This research has five major strengths.

1. This is the first study to examine the relationship between socio-ecological factors and malaria in the identified high risk areas in Yunnan Province, China.

2. This is the first attempt to detect and identify cluster areas of malaria deaths in China, and to estimate the effects of socio-ecological factors on malaria in high risk areas in Yunnan.

3. A complex set of variables including climatic, demographic, economic and ecological variables were used in this study, covering a long period of 20 years (1991–2010) at a county level and detailed information on weekly climate variables and malaria cases were incorporated in the model. The finer spatial and temporal scale datasets for malaria deaths/cases which integrated with multiple socio-ecological variables ensured a sufficiently high statistical power.

4. Sophisticated spatial and temporal approaches such as GIS, SaTScan and DLNM were applied in this study. These methods have a great potential to be further used in the research of malaria and other mosquito-borne diseases.

5. Research outcomes of this study may have important implications for public health authorities in the decision–making and the development of effective intervention strategies to control and prevent the wide spread of malaria infection.

7.5 Limitations of the study

There are two major types of limitations in the study, which include possible information bias and confounding factors.

1. Information bias

Malaria is a notifiable infectious disease in China. Under-reporting is possible, which is an important source of information bias. Under-reporting is likely to occur when people who are infected by the malaria parasite with clinical symptoms, but do not seek medical treatment as they only buy some medicines for themselves instead, and/or when people living in remote rural mountain areas cannot access to the health care facilities. Another potential source of under-reporting is that people who are asymptomatic but having malaria parasites in their body due to the long term incubation period of plasmodium parasite (e.g. *P.vivax*) will not choose to seek a doctor (Ministry of Health of the People's Republic of China 2006). To avoid this kind of information bias, both passive and active case detection surveillance are provided in China. Daily internet reporting is available in China since 2005. National survey is carried out in hospitals in November of each year to identify the proportion of notifiable diseases that went unreported. In addition, a house-to-house survey is conducted every three years to find out under-reporting cases of surveillance diseases and adjust for the reporting rate to avoid the bias caused by cases and deaths outside the reporting system.

Malaria diagnosis is also imperfect due to a confusion of parasite strains of *P. vivax* and *P. falciparum* and other diseases with similar clinical symptoms (e.g. fever) (Clements *et al.* 2009). The misdiagnosis is possible because different examiners may have different experiences, even when using the same diagnosis criteria. Some malaria cases are diagnosed by microscope and others by rapid diagnostic test or by clinical symptoms. The misdiagnosis bias can be minimized by providing the training program for local physicians on malaria diagnosis techniques.

As malaria data in Yunnan were reported by different health staff in different locations over different observation periods. The locations of malaria cases diagnosed may differ from those where they are infected by the disease. This is particularly evident in peak seasons, i.e. autumn and summer, where bias is to be expected. However, information bias of such kind is unlikely to have a significant impact on the results of this study, because the data quality is unlikely to change remarkably on the weekly/monthly basis.

In chapter 6, 16-year annual data were used and it may be too short and crude to estimate the impact of some predictors (e.g rainfall) on the transmission of malaria.

2. Confounding factors

A number of potential confounders may affect the assessment of the relationship between climatic, socio-economic and ecological variables and the transmission of malaria infection. These potential confounders include mosquito control measures, drug resistance, housing conditions, human activities, population immunity and individual behaviour. These factors may impact the transmission dynamics of malaria, but the detailed data on these factors were unavailable in this study.

7.6 Recommendations

Based on the results of this study, I would like to make the following recommendations (Figure 7.2).

7.6.1 Disease and vector surveillance and monitoring

The results of this study indicate that the high risk area of malaria deaths has been persisting along the China-Myanmar border in western Yunnan over the past two decades. The chloroquine-resistance of *P. falciparum* in western Yunnan is responsible for this concentrated cluster of malaria deaths (Yang *et al.* 2008). The use of effective antimalarial drugs will be important to decrease clinical cases and to prevent more deaths in Yunnan. The regular surveillance of drug resistance to *P. falciparum*, insecticide resistance to vector(s), and local mosquito vector(s) surveillance should be strengthened in this area. The strengthening of surveillance mechanism can provide valuable information for prevention of malaria epidemic, improvement of control measures and evaluation of public health intervention. More attention of malaria surveillance should be given to both local residents and mobile population across international border in Yunnan.

7.6.2 Public health interventions

The current public health interventions can be improved by: 1) using new techniques such as GIS and spatial analysis to identify and monitor high risk areas/hot spots of malaria infection; 2) providing timely and feasible malaria control measures to hot spots; 3) educating people to protect themselves from malaria infection and training health workers to improve their skills in case diagnosis and treatment, to implement vector control programs and to undertake risk management of outbreaks; 4) cross-sector cooperation between different departments (e.g. entry-exit inspection and quarantine bureau, industrial and commercial bureau, border police, tourism agency and farm management) and collaborating with the neighbouring countries (e.g. Myanmar, Laos and Vietnam) for the control and elimination of border malaria.

7.6.3 Health education and training

It is important to conduct health promotion and community education and training to reduce the transmission of malaria in the identified high risk areas in Yunnan. Health education targeting primary and secondary school students, farmers and mobile population, particularly those coming from another province or from a low-immunity area along the border areas should be regularly carried out (Xu *et al.* 1997). The training of primary health care workers is necessary to improve their skills in the diagnosis and to allow rapid and formal treatment to be given to malaria patients.

7.6.4 Future research directions

To better understand the transmission dynamics of malaria, detailed spatio-temporal epidemiological research is needed in Yunnan Province. In the identified primary and secondary cluster areas (e.g. western and southern Yunnan), there is a need to further examine the effects of other risk factors on malaria transmission, such as mosquito vectors, land use, drug resistance to *P. falciparum* and mobile populations across the border. The examination of the threshold of temperature and rainfall and its roles in malaria transmission also needs to be explored in order to develop the preliminary MEWS. Our results show that income was negatively associated with the malaria incidence in Mengla County. The influence of income on malaria in other high risk areas needs to be further evaluated. More research on the different socio-ecological determinants of local and imported malaria cases is necessary, particularly along three border areas (e.g. China-Myanmar, China-Laos and China-Vietnam). These researches are important to facilitate the malaria elimination program in Yunnan border. Such work could provide important data for health authorities to plan and conduct health education programs to protect the vulnerable populations and to reduce the risk of malaria infection throughout the whole province.

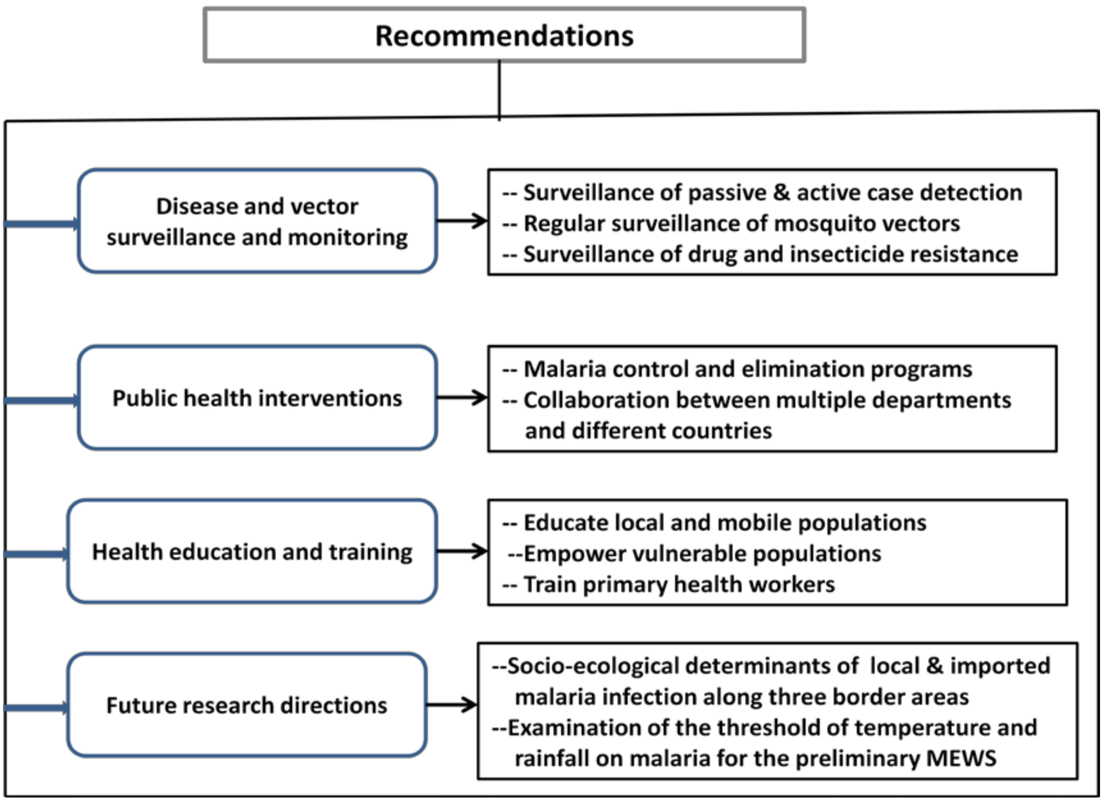

Figure 7.2 Recommendations for public health, policy, practice and research

7.7 References

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Appendices

Appendix A

Ethics approval

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-----Original Message-----
From: Research Ethics [mailto:ethicscontact@qut.edu.au]
Sent: Thursday, 19 August 2010 1:18 PM
To: YAN BI
Cc: QUT Research Ethics Unit; Shilu Tong
Subject: Ethics Application - Confirmed as Exempt

Dear Ms Yan Bi

Project Title: Socio-ecological variability and malaria transmission
               in Yunnan Province, China
Ethics Category:  Human
Status:           Exempt
Exempt Number:    1000000573

This email is to advise that your application has been reviewed by the
Chair, University Human Research Ethics Committee (UHREC) and deemed as
exempt from the need for HREC review, approval and monitoring in
conformity with sections 5.1.22 and 5.1.23 of the National Statement on
Ethical Conduct in Human Research (2007).

Please note that since this exemption has been granted, responsibility
for ensuring that the project is conducted in accord with the National
Statement, with relevant legislation and with QUT policies still rests
with you, the investigator, and responsibility for monitoring
compliance rests with your Supervisor and/or Head of School.  Please
inform your Supervisor and/or Head of School of any changes to the
study protocol, also informing UHREC, via the Research Ethics Unit, if
the study protocol changes in ways that might affect this exemption in
any way, for example altering risks or the usage of personal
information.

Please also note you are required to keep an auditable record of any
human research that is exempted from ethical review as required by
section 5.2.9 of the National Statement.

Please note that exemption is not equivalent to approval and therefore
care must be taken to accurately describe the conditions under which
this study has been reviewed.  UHREC recommends the following statement
be used when drafting manuscripts for publication:

"The QUT University Human Research Ethics Committee assessed this
research as meeting the conditions for exemption from HREC review and
approval in accordance with section 5.1.22 of the National Statement on
Ethical Conduct in Human Research (2007)."

Should you have any further queries please do not hesitate to contact
the Research Ethics Unit on 3138 5123.
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Regards

Janette Lamb on behalf of the Chair UHREC
Research Ethics Unit | Office of Research
Level 4 | 88 Musk Avenue | Kelvin Grove
p: +61 7 3138 5123
e: ethicscontact@qut.edu.au

Appendix B
Data permission

云南省疾病预防控制中心

Statement

16/07/2010

To whom it may concern,

Ms Yan Bi, a PhD candidate at School of Public Health of QUT, Australia, is now a staff of Yunnan Center for Disease Control and Prevention, China. We are pleased to welcome Ms Yan Bi to go back to do her PhD research data collection in Yunnan province. We are going to support her to collect data from Yunnan CDC with non-identifiable disease case and from other departments like Statistical Bureau of Yunnan Province and Mengla County, China.

Sincerely,

Yours,

云南省疾病预防控制中心

Yunnan Center for Disease Control and Prevention, China

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